The Journal of International Medical Research
2000; 28: 149 – 167

Pharmacokinetics of Orally and Intravenously Administered Telmisartan in Healthy Young and Elderly Volunteers and in Hypertensive Patients

J STANGIER, CAPF SU AND W ROTH

Boehringer Ingelheim Pharma KG, Biberach, Germany

A series of studies was conducted in healthy young males and healthy elderly males or females to evaluate the pharmacokinetic profile of telmisartan. In addition, two phase-II clinical trials assessed the pharmacokinetics and the safety of telmisartan in mild-to-moderate hypertensive patients. Telmisartan was given as a single oral (1 – 160 mg) or intravenous (10 – 160 mg) dose to young males. In another multiple-dose study, telmisartan 320 mg was administered orally once daily for 7 days to healthy young male subjects. Elderly subjects received oral telmisartan (20 and 120 mg) once daily for 7 days. Telmisartan doses of 10, 20, 40, 80, 120 and 160 mg were taken once daily by mild-to-moderate hypertensive patients for 7 days. Additionally, oral telmisartan (40, 80 or 120 mg) was administered once daily for 28 days to hypertensive subjects. Following oral dosing, median time to maximum plasma telmisartan concentration was 0.5 – 2 h, with maximum plasma concentrations increasing disproportionately with dose. By contrast, plasma concentrations were directly related to the intravenous dose. Steady state was observed after 5 – 7 days of once-daily administration, and there was no clinically relevant accumulation at 28 days. The plasma concentration–time profiles were similar in all study groups and were characterized by fast absorption and a rapid biexponential decline after the peak plasma concentration, with a prolonged terminal elimination phase (> 20 h in

healthy and hypertensive subjects). Telmisartan was well tolerated, with a low incidence of drug-related adverse events. The most frequent event was headache, which also occurred in placebo-treated control subjects. No changes in heart rate, electrocardiograms or clinical chemistry were detected following receipt of telmisartan. The study thus shows that high systemic levels of telmisartan, which are well tolerated, can be attained in healthy adults of any age and in hypertensive subjects. The long terminal elimination half-life makes telmisartan suitable for once-daily dosing and contributes to the sustained efficacy over the full 24-h dosing interval.

KEY WORDS: TELMISARTAN; PHARMACOKINETICS; AT_1 RECEPTOR ANTAGONIST; HYPERTENSION; TOLERABILITY

INTRODUCTION

Angiotensin II is produced either systemically or in local tissue by the renin–angiotensin–aldosterone (RAA) cascade.[1] Angiotensinogen synthesized by the liver is first converted to the physiologically inactive decapeptide angiotensin I in the presence of renin, which is generated in the juxtraglomerular apparatus of the kidney. In the presence of angiotensin converting enzyme (ACE), physiologically active angiotensin II is formed. The conversion of angiotensin I to angiotensin II, however, is not exclusively catalysed by ACE, and other enzymes can also generate angiotensin II from angiotensin I. Because angiotensin II acts directly on the smooth muscle of the arterioles, it plays an important direct role in hypertension. Angiotensin II also indirectly induces hypertensive effects due to its stimulation of aldosterone production, which in turn brings about sodium, chloride, and water retention by the kidneys.[2,3] In addition, proliferation of vascular and cardiac cells is mediated through angiotensin II at the angiotensin II subtype 1 (AT_1) receptor.[4] The sustained actions of angiotensin II may contribute to the long-term harmful effects of hypertension, including the development of myocardial hypertrophy, heart failure and renal disease.[5]

An appreciation of the importance of the direct and indirect hypertensive actions of angiotensin II resulted in the development of antihypertensive drugs that target the RAA cascade and regulate the activity of angiotensin II. One class is the ACE inhibitors, which prevent the formation of angiotensin II.[6] However, because angiotensin II can be formed by other enzymes, some angiotensin II will still be generated.[7] A further disadvantage of ACE inhibitors is that their mode of action is non-specific; they also block the conversion of the structurally related compounds bradykinin and substance P to physiologically inactive compounds. The resultant elevated levels of these peptides are probably responsible for the dry, persistent cough experienced by many patients treated with ACE inhibitors.[8–11] An alternative approach to therapy is the

blockade of the interaction of angiotensin II with AT_1 receptors, which are believed to mediate its physiological actions.[12] The use of angiotensin II antagonists has two advantages over ACE inhibitors. First, they do not affect bradykinin and substance P levels, and hence their use would overcome the problem of the troublesome cough frequently associated with ACE inhibitors.[13,14] Secondly, as well as blocking the systemic effects of angiotensin II, they also act at the local tissue level.

Telmisartan is a new non-peptide angiotensin II receptor antagonist available for treatment of hypertension. Clinical studies indicated that telmisartan produces a sustained reduction in blood pressure for more than 24 h after once-daily dosing, with a side-effect profile comparable to that of placebo.[15 – 22] Telmisartan is not a prodrug and, therefore, does not need to be converted into an active principle, as in the case of losartan or candesartan cilexetil.[23] The telmisartan molecule contains one acidic and two basic centres.[24] Due to hetero-aromatic substituents in the benzimidazole nuclear structure the molecule is highly lipophilic, with an apparent partition coefficient between *n*-octanol and buffer of 3.2. The lipophilicity of telmisartan enables it to achieve high tissue penetration.[25] In conjunction with very rapid membrane transport kinetics, the compound is well suited for fast access to the receptor binding sites. Also, selective and high-affinity binding to AT_1 receptors results in potent and long-lasting, but reversible angio-tensin II antagonism.

In order to evaluate the absorption, distribution, metabolism and excretion of telmisartan, a study was conducted in healthy male subjects using [^{14}C]telmisartan administered as an oral solution and as a short-duration intravenous (IV) infusion.[26] Measurement of total ^{14}C in plasma after oral and IV administration showed that the mean absorption of orally administered telmisartan was 50% and that, on average, 84% of the total radioactivity in plasma reflected the parent compound. The remainder could be ascribed to the glucuronide of telmisartan, which is the only metabolite identified in man. The major part of the radioactivity was excreted within 120 h after oral or IV administration, and recovery of radioactivity was complete after 144 h. The urinary excretion of radioactivity was insignificant (the cumulative urine excretion was < 2% of the dose for both routes of administration), and virtually all of the administered dose was excreted in faeces as the parent compound.

This article is a compilation of a series of studies carried out to characterize further the pharmacokinetic profile of telmisartan, given as single or repeated doses and administered either by the oral or IV route, in healthy, normotensive young adult males, normotensive elderly subjects of either gender, and in patients with mild-to-moderate hypertension. Telmisartan plasma concentration–time curves were used to determine single-dose and steady-state pharmacokinetic parameters. Absolute bioavailabilities of oral formulations, in relation to IV dosing, relative bioavailability of oral formulations and the degree of protein binding were also evaluated. These studies, in addition, monitored the safety of telmisartan in the different study populations.

SUBJECTS AND METHODS

SUBJECTS

The studies were conducted in three different populations: healthy, normotensive (diastolic blood pressure [DBP] < 100 mmHg) Caucasian males (age range

18 – 50 years) who were within 15% of normal body weight for height; healthy, normotensive (supine morning DBP 60 – 100 mmHg) elderly (age > 64 years) Caucasian males or females with a resting heart rate of 45 – 100 beats per min; and males and sterile or post-menopausal females (18 – 60 years; within 20% of normal body weight according to height and frame) of any race who were hypertensive (supine BP 100 – 114 mmHg at the end of a 4-week placebo run-in and not varying by > 10 mmHg) or hypertensive as defined by a morning systolic blood pressure (SBP) of < 200 mmHg together with a DBP in the range 95 – 114 mmHg measured after 5 min in the supine position following a 4-week placebo washout. Written informed consent was required before any subject could be enrolled.

The exclusion criteria that applied to all study populations were: daily smoking of > 15 cigarettes, three cigars or three pipes; inability to refrain from smoking while in the study centre; alcohol or drug dependency; history of gastrointestinal, hepatic, renal, metabolic or hormonal disease; gastrointestinal surgery (except appendectomy); drug allergy or hypersensitivity; blood donation within the previous month; hepatitis B- or HIV-positive; excessive physical activity (i.e. sports or hard labour) ≤ 2 weeks before and/or during the study; and participation in another study within the previous 2 months. Any otherwise healthy subject with a clinically relevant deviation in 12-lead electrocardiogram (ECG) or who had received any medication in the 10 days before the start of the study was excluded. Further exclusion criteria especially applicable to the hypertensive subjects were: known secondary hypertension; low- or high-salt diet; serum aspartate aminotransferase or alanine aminotransferase activity exceeding twice the upper limit of normal; serum creatinine > 2.3 mg/dl; New York Heart Association congestive heat failure functional class II – IV; myocardial infarction ≤ 6 months before; and clinically relevant cardiac arrhythmia, angina, or insulin-dependent diabetes mellitus. These subjects were also not allowed to receive any of the following medications during the study: antihypertensives (other than telmisartan); digitalis; antacids; H_2 blockers; gastrointestinal motility agents; cholestyramine; colestipol; non-steroidal anti-inflammatory agents; systemic corticosteroids; antianginal agents; and anticoagulants. Concurrent diuretics for indications other than hypertension were permitted, but no subject could be included who had received a diuretic within the preceding 3 months.

STUDY DESIGN

All studies were approved by local ethics committees and conformed to the requirements of the revised Declaration of Helsinki. Pre-dosing screening was conducted to confirm that all subjects conformed with the entry requirements. At this stage, vital signs (blood pressure, 12-lead ECG and heart rate) were evaluated, and blood and urine samples were collected for clinical laboratory tests.

The studies were conducted in clinical investigation units, which the subjects entered the night before pharmacokinetic evaluations were performed. Subjects remained within the unit until the last post-dose blood sample had been collected.

The dose-ranging oral and IV studies conducted in healthy young males were randomized, placebo-controlled, and open-label with respect to the dose given, but double-blind within each dose with respect to the receipt of telmisartan or placebo. The bioavailability studies conducted in healthy young males were three-way (IV solution,

oral solution, tablet), crossover and open-label in design. Evaluation of the pharmacokinetics in healthy elderly subjects was performed using an open-label, crossover study. The design of the studies conducted in hypertensive subjects was randomized, double-blind, active- or placebo-controlled, with a 4-week placebo run-in period (for washout of previous antihypertensive medication) before the administration of telmisartan.

On completion of telmisartan administration, the vital signs were re-evaluated and clinical laboratory tests repeated in all subjects.

TELMISARTAN ADMINISTRATION

In the first study in healthy young male subjects, single oral doses of telmisartan (1 – 160 mg) were given as freshly prepared drinking solution containing γ-cyclodextrin as excipient; each dose was administered to three healthy young male volunteers and a fourth subject received matching placebo. The oral dose of 320 mg, given as four 80-mg tablets with 150 ml tap water once daily for 7 days, was received by a further 10 healthy young males to evaluate steady-state pharmacokinetics; two other subjects received matching placebo once daily for 7 days.

Other healthy young males (four subjects per dose) received a single IV dose of telmisartan (10 – 120 mg), infused over 30 min, and a total of 12 volunteers received placebo infusion. In two separate studies conducted with the primary purpose of determining the absolute and relative bioavailabilities, telmisartan 40 mg (n = 12) and 160 mg (n = 12) was administered as tablets, an IV infusion over 30 min, and as an oral solution containing γ-cyclodextrin, with a washout period of 14 days between the administrations. The data from the IV phase of these two studies were also used to assess the IV pharmacokinetics of telmisartan.

A total of 14 elderly normotensives were enrolled to receive both telmisartan 20 mg and 120 mg in tablet form taken with 150 ml water once daily for 7 days. There was a washout period of 14 days between receipt of the two doses. This study was not placebo-controlled.

A phase-II study, with the objectives of assessing the dose–response relationship, multiple-dose safety/tolerability, pharmacokinetics, and dose proportionality of telmisartan, was conducted as a double-blind, randomized, active- and placebo-controlled trial. A total of 80 hypertensive patients of either gender received escalating doses of telmisartan (10, 20, 40, 60, 80, 100, 120 and 160 mg) in drinking solution once daily for 7 days. At each of the eight doses, ten patients were randomly assigned to the telmisartan, active control (enalapril 20 mg) or placebo in a ratio of 6:2:2.

Other hypertensive patients were randomized to receive telmisartan capsules at a dose of 40 mg (n = 40), 80 mg (n = 40) or 120 mg (n = 41), or matching placebo (n = 43) administered once daily for 28 days; the medication was taken with 120 ml water. The aims of this study were to assess the dose–response relationship, safety/tolerability, and pharmacokinetics of telmisartan.

In both single- and multiple-dose oral studies, telmisartan was given to overnight-fasted subjects and no food was allowed for at least 1 h after dosing; thereafter, a breakfast was provided. When administered IV, telmisartan was infused 90 min after a standard breakfast. The duration of infusion was 30 min. In all studies, the subjects received standardized meals and snacks while confined to the clinical investigation unit. During this time, the consumption of alcohol or caffeine-containing drinks and smoking were not allowed.

SAMPLE COLLECTION

Venous blood samples (5 – 10 ml) were collected, using EDTA as anticoagulant, immediately prior to telmisartan administration and at intervals for 48 – 96 h after the completion of dosing. Plasma was isolated by centrifugation (3500 rpm for 30 min) and samples were stored at –20˚C until determination of telmisartan concentrations. In some studies, urine samples were collected over the periods of 0 – 6, 6 – 12 and 12 – 24 h; volumes collected were recorded and were related to fluid intake. Pooled urine samples were stored at –20˚C until analysis.

TELMISARTAN ANALYSIS

After stored urine and plasma samples had been thawed, telmisartan was measured by validated high-performance liquid chromatographic (HPLC) methods with fluorescence detection (excitation wavelength 300 nm; emission wavelength 385 nm). The lower limits of quantitation were 0.1 – 1.0 ng/ml.

Glucuronic acid conjugates of telmisartan in urine were cleaved by incubation with β-glucuronidase/arylsulphatase for 18 h at 37°C prior to determination of telmisartan by HPLC.

PHARMACOKINETIC AND STATISTICAL ANALYSIS

Pharmacokinetic parameters were generally determined using non-compartmental methods.

After single-dose administration, the following pharmacokinetic parameters for telmisartan were derived: maximum concentration in plasma (C_{max}), obtained directly from the measured data; time at which the maximum concentration was observed (t_{max}); area under the plasma concentration–time curve between dosing (time 0 h) and 24 h (AUC_{0-24}); area under the plasma concentration–time curve between time 0 h and infinity ($AUC_{0-\infty}$); and the terminal elimination half-life ($t_{1/2}$) calculated from the estimated elimination rate constant (k_{el}) by linear regression of the log of the plasma concentrations as $\ln 2/k_{el}$. The AUCs were calculated using the log-linear trapezoid rule. In addition, in one oral study in hypertensive patients, the mean residence time (MRT) and apparent volume of distribution during the terminal elimination phase after dosing (V_z/f) were determined.

In the subjects receiving telmisartan once daily for 7 or 28 days, the following steady-state pharmacokinetic parameters were determined: $C_{max,ss}$, AUC_{ss}; and the minimum (trough) plasma concentration (C_{min}) obtained immediately before the administration of telmisartan on day 7 or 28.

The total clearance (CL_{tot}) following IV administration or CL_{tot}/f following oral dosing was determined in all studies.

Arithmetic means were used to construct plasma concentration–time curves. Geometric means and geometric coefficients of variation were calculated for all pharmacokinetic parameters, with the exception of t_{max}, which was expressed as the median value.

Accumulation ratios (R_A) were determined from the ratio of AUC_{ss}/AUC_{0-24} or $C_{max,ss}/C_{max,day\ 1}$. The ratios of AUC for IV versus tablet and IV versus oral solution were employed to calculate absolute bioavailability (f) using the following formula:

$$\text{absolute bioavailability (\%)} = (AUC_{0-\infty,tablet}/AUC_{0-\infty,IV}) \times 100.$$

Relative bioavailability of tablet versus oral solution was established on the basis of $AUC_{0-\infty}$ ratios as follows:

$$\text{relative bioavailability (\%)} = (AUC_{0-\infty,tablet}/AUC_{0-\infty,solution}) \times 100.$$

For most studies, the doses given were unblinded and also the number of subjects evaluated in different groups was small;

thus, results were only interpreted descriptively.

PLASMA PROTEIN BINDING

An equilibrium dialysis device was employed to determine plasma protein binding. Plasma isolated from blood samples taken from elderly subjects 30 min before telmisartan administration on day 7 at doses of 20 and 120 mg was mixed with telmisartan and then dialysed against 0.01 M phosphate buffer. Concentrations of telmisartan on either side of the semipermeable membrane were determined by HPLC.

SAFETY EVALUATION

In addition to monitoring any changes in blood pressure, heart rate, 12-lead ECG and clinical laboratory abnormalities, any adverse events reported by the subjects during the studies were recorded. Information on the intensity, likely causality, duration and outcome of all adverse events was also noted.

RESULTS

PHARMACOKINETICS IN HEALTHY YOUNG MALES AFTER ORAL DOSING

The pharmacokinetic profile of oral telmisartan was investigated when given as a single dose (1 – 160 mg) or as multiple doses (320 mg) once daily for 7 days.

In the 'first-in-man' increasing-dose study performed in healthy young male subjects, in order to characterize the tolerability and pharmacokinetics, single oral doses (1, 2.5, 5, 10, 20, 40, 60, 80, 100, 120 and 160 mg) of telmisartan were administered as solution with γ-cyclodextrin as excipient. Three subjects were randomly assigned to receive telmisartan and one subject per dose-group received placebo. Telmisartan was rapidly absorbed at all doses; the median time to peak plasma concentrations (i.e. t_{max}) was 0.5 – 3 h. Values for C_{max} and AUC increased supraproportionally with doses of > 40 mg. The geometric mean $t_{1/2}$ at the 40-mg dose was 15.5 h. This is based on a limited number of blood samples obtained from only three subjects and only up to 48 h after dosing; the $t_{1/2}$ values for the other doses were not calculated because of insufficient data points in the terminal elimination phase.

Urine samples were collected from healthy young male subjects receiving the 160-mg dose. Analysis of these samples showed that free, non-conjugated telmisartan in urine accounted for < 0.01% of the administered dose. Beside the parent compound, the glucuronide of telmisartan was found in urine. The excreted fraction of telmisartan calculated after glucuronidase/sulphatase cleavage of the conjugate represented < 1% of the dose.

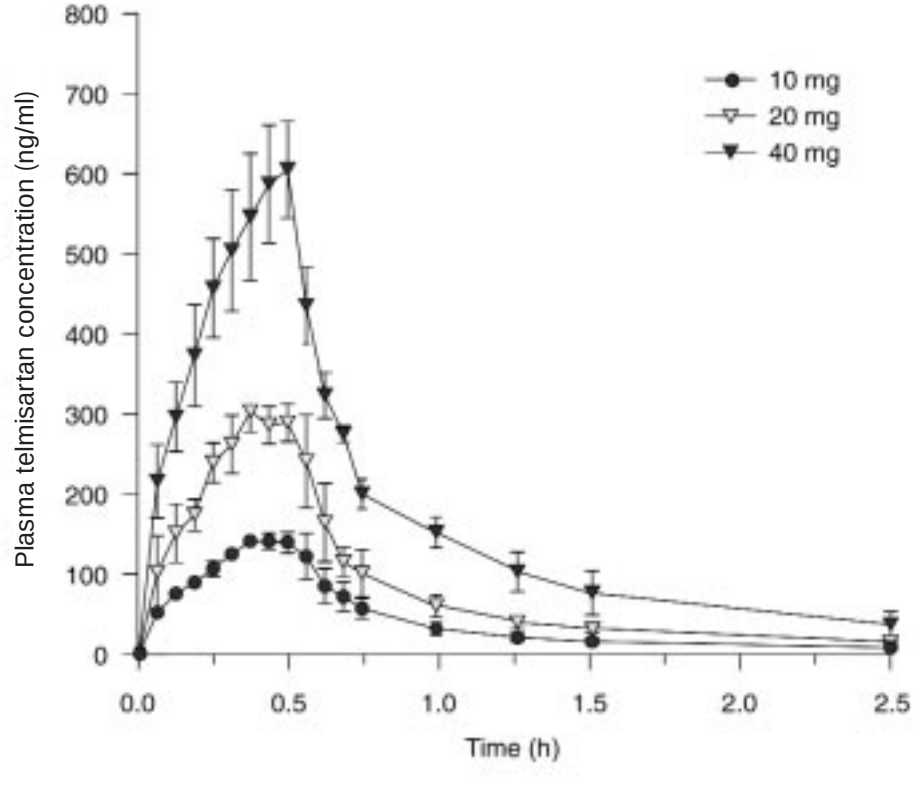
In order to explore further the tolerability and pharmacokinetics of telmisartan following multiple-dose administration, a very high dose of telmisartan (320 mg) was administered once daily for 7 days to 10 healthy male subjects; two additional subjects received placebo. For evaluation of the plasma concentrations, frequent blood samples were collected on days 1 and 7 of dosing, at trough immediately before drug intake on days 2 – 7, and in the washout phase up to 96 h after the final dose. At day 1 of telmisartan administration, plasma concentrations increased rapidly after dosing and C_{max} (≤ 7.5 µg/ml) was detected 0.5 – 1.0 h after drug intake. Thereafter, there was a rapid distribution phase, with an estimated distribution half-life of about 0.5 h. Within 3 – 4 h of dosing, plasma concentrations returned to low levels. This rapid distribution was followed by a prolonged elimination phase, but no appreciable drug accumulation was observed. Trough plasma concentrations ranged between 7 and 85 ng/ml, and variable steady-state maximum plasma concentrations

of between 1.1 and 10.3 µg/ml were detected, with a geometric mean $C_{max,ss}$ of 4.6 µg/ml, compared with 3.3 µg/ml after the first dose. The AUC_{ss} and AUC_{0-24} were 6.1 and 4.3 µg·h/ml, respectively. The geometric mean $t_{1/2}$ of telmisartan in this trial was 25 h.

PHARMACOKINETICS IN HEALTHY YOUNG MALES AFTER IV INFUSION

Telmisartan pharmacokinetics after IV infusion were evaluated in the dose range 10 – 160 mg. Mean plasma concentration–time profiles after infusion of telmisartan 10, 20 and 40 mg over 30 min are shown in Fig 1. After cessation of the infusion, plasma telmisartan concentrations declined rapidly in a polyexponential manner, with a marked α-phase in the first hour. As observed following oral administration, the rapid distribution phase was followed by slow elimination. The pharmacokinetic parameters, derived by non-compartmental analysis, are summarized in Table 1. Plasma clearance of telmisartan was high (CL_{tot} > 800 ml/min), and the mean volume of distribution (V_{ss}) of 460 – 510 l indicates distribution of telmisartan into the tissue compartment. Over the dose range

FIGURE 1



Plasma concentration–time profiles (means ± SD) of telmisartan in healthy male volunteers after administration of 10, 20 and 40 mg (n = 4) as an intravenous infusion over 30 min.

TABLE 1

Pharmacokinetics (geometric means and percentage coefficient of variation) of single-dose intravenous telmisartan in healthy young male volunteers

Parameter	10 mg (*n* = 4)	20 mg (*n* = 4)	40 mg (*n* = 4)	40 mg (*n* = 12)[b]	80 mg (*n* = 4)	120 mg (*n* = 4)	160 mg (*n* = 12)[b]
C_{max} (ng/ml)[a]	150; 5%	309; 8%	616; 11%	623; 19%	1315; 21%	1773; 16%	3200; 24%
$AUC_{0-\infty}$ (ng · h/ml)	ND	ND	744; 38%	706; 24%	1566; 31%	2494; 46%	3320; 42%
$t_{1/2}$ (h)	ND	ND	18.5; 11%	22.6; 40%	22.3; 30%	19.0; 31%	17.7; 28%
CL_{tot} (ml/min)	ND	ND	896; 38%	944; 25%	851; 31%	802; 46%	803; 42%

ND, not determined.

[a]Plasma concentraton at the end of infusion (29 min).

[b]Primary purpose of this study was to determine bioavailabilities.

10 – 120 mg, $AUC_{0-\infty}$ and C_{max} increased dose proportionally, and geometric mean C_{max} values varied between 150 ng/ml for the 10-mg dose and 1773 ng/ml for 120 mg. A dose-proportional increase in $AUC_{0-\infty}$ over the range 40 – 120 mg was also observed. For the 160-mg dose, which was administered to 12 subjects in a separate study performed primarily to determine absolute bioavailability, the mean C_{max} was 3200 ng/ml.

ABSOLUTE AND RELATIVE BIOAVAILABILITY

The absolute bioavailability of the telmisartan tablet formulation was determined at the 40- and 160-mg doses. Based on AUC ratios, the bioavailabilities of the 40-mg tablet and solution were 42.4% and 47.3%, respectively, when the dose was administered orally and by IV infusion to healthy young males. At the 160-mg dose, the absolute bioavailabilities of the tablets (two 80-mg tablets administered) and oral solution were 57.4% and 57.5%.

PLASMA PROTEIN BINDING

Investigations to characterize the binding parameters of the relevant proteins with [^{14}C]telmisartan were performed by incubation at 37°C and subsequent equilibrium dialysis. These studies showed that, in serum, 99.5% of telmisartan was bound at concentrations of 0.5 and 5 µg/ml, and the main serum protein involved was human serum albumin (Table 2). Telmisartan also displayed saturable binding to α-1-acid glycoprotein and non-saturable binding to γ-globulin. Binding of telmisartan to lipoproteins was also significant.

PHARMACOKINETICS IN THE ELDERLY AFTER ORAL DOSING

The pharmacokinetic profile of telmisartan 20 and 120 mg administered once daily for 7 days to six male and six female healthy elderly subjects was evaluated in a multiple-dose, open-label, two-way crossover study. The mean age of subjects in this study was 70 years (range 65 – 78 years). The geometric mean C_{max} at day 1 after administration of telmisartan 20 mg was 17.9 ng/ml (Table 3) and the $C_{max,ss}$ was 28.3 ng/ml, yielding an R_A (i.e. $C_{max,ss}$ divided by $C_{max,day\ 1}$) of 1.6. The median t_{max} was 0.5 h. At day 1, AUC_{0-24} was 159 ng·h/ml and AUC_{ss} was 287 ng·h/ml,

TABLE 2

Binding percentages of telmisartan to serum and serum proteins

	Binding percentages ± SD	
Protein	**0.5 µg/ml**	**5 µg/ml**
Serum	99.76 ± 0.09%	99.59 ± 0.05%
Human serum albumin	99.92 ± 0.01%	99.81 ± 0.06%
α-1-acid glycoprotein	77.83 ± 4.03%	54.34 ± 4.37%
γ-Globulin	55.99 ± 3.11%	53.69 ± 1.26%
High-density lipoprotein	93.48 ± 0.58%	91.78 ± 0.47%
Low-density lipoprotein	68.76 ± 4.69%	63.02 ± 0.29%
Very-low-density lipoprotein	26.84 ± 3.77%	18.40 ± 0.11%

corresponding to an R_A of 1.8. The geometric mean $t_{1/2}$ was 36.4 h, with individual values ranging between 19.4 and 64.1 h. The mean value for CL_{tot}/f was 1160 ml/min.

At the 120-mg dose, a mean C_{max} of 533 ng/ml was observed at day 1 (Table 3). After repeated once-daily administration, the mean $C_{max,ss}$ was 592 ng/ml. The mean AUC increased moderately from 1420 ng·h/ml at day 1 to 2200 ng·h/ml at steady state (day 7); thus, the R_A was 1.55. The median t_{max} at steady state was 1 h. Individual values for $t_{1/2}$ were in the range 18.0 – 91.8 h, with a geometric mean value of 37.2 h that was independent of dose. The mean total clearance (CL_{tot}/f) was 909 ml/min.

TABLE 3

Pharmacokinetics (geometric means and percentage coefficient of variation) of oral telmisartan in normotensive elderly subjects

	Single dose		Steady state	
Parameter	**20 mg (*n* = 12)**	**120 mg (*n* = 12)**	**20 mg (*n* = 12)**	**120 mg (*n* = 12)**
C_{max} (ng/ml)	17.9; 42%	533; 102%	28.3; 66%	592; 147%
t_{max} (h)	0.5[a]	0.75[a]	0.5	1.00
AUC_{0-24} (ng · h/ml)	159; 64%	1420; 80%	287; 85%	2200; 86%
$t_{1/2}$ (h)	ND	ND	36.4; 43%	37.2; 54%
CL_{tot}/f (ml/min)	ND	ND	1160; 85%	909; 87%

ND, not determined.
[a]Median value.

The daily measurement of C_{min} values confirmed that steady-state conditions were reached within the administration period of 7 days. In the case of $C_{max,ss}$, there was a non-proportional increase with dose: at the 120-mg-dose level, mean $C_{max,ss}$ was 3.5 times higher than would be expected if linear kinetics were assumed. With regard to AUC_{ss}, the increase was 1.3-fold. Therefore, the non-proportional increase in AUC was smaller than in the case of C_{max}.

The protein binding of telmisartan was assessed by equilibrium dialysis. Comparison of data obtained from younger subjects revealed that there is no decrease in protein binding of telmisartan in elderly subjects.

In the 120-mg-dose group, a prominent gender effect with regard to C_{max}, $C_{max,ss}$ and, to a smaller extent, for AUC_{0-24} and AUC_{ss} was observed. The geometric mean values for C_{max} and $C_{max,ss}$ were more than three-fold higher in females than in males, whereas AUC_{0-24} and AUC_{ss}, respectively, were 1.6- and 1.2-fold higher in females than in males. By contrast, at the 20-mg-dose level, no relevant gender effect was observed.

PHARMACOKINETICS IN HYPERTENSIVE PATIENTS

In an early clinical trial performed in hypertensive patients, telmisartan doses of 10, 20, 40, 60, 80, 100, 120 and 160 mg were administered as an oral γ-cyclodextrin solution once daily for 7 days. At each dose level, 10 patients were randomly assigned to telmisartan, enalapril 20 mg, or placebo in the ratio of 6:2:2. High interindividual variability of plasma concentrations was observed in this study, and there was a disproportionate increase in C_{max} and AUC with increasing dose (Table 4). This disproportionality was most prominent with regard to C_{max}. Mean plasma concentration–time profiles of telmisartan after administration of the 20-, 40- and 80-mg doses available for treatment of hypertension are depicted graphically in Fig. 2. Arithmetic mean $t_{1/2}$ values, which were in the range 18.4 – 55.3 h, were independent of dose. An R_A of 1.5 – 2.0 was observed. More importantly, trough values were low in relation to C_{max} and did not exceed 230 ng/ml, even after repeated administration of telmisartan 160 mg.

The second phase-II trial with a pharmacokinetic component was a 4-week group-comparison study in mild-to-moderate hypertensive patients, utilizing telmisartan doses of 40, 80 and 120 mg given as a capsule formulation. The patients were randomized to receive either placebo, active control (enalapril 20 mg), or telmisartan once daily for 28 days, each treatment group comprising 40 – 41 patients. Pharmacokinetic parameters, which are presented in Table 5, demonstrated that steady-state levels were achieved within 7 days of the start of dosing. Again, high intersubject variability in plasma concentrations was observed. The mean $AUC_{0-\infty}$ was nearly dose-proportional, increasing two-fold for a doubling of the dose from 40 to 80 mg, and increasing 1.6-fold with a 1.5-fold increase in dose from 80 to 120 mg. Peak plasma concentrations increased disproportionately with dose, but the $t_{1/2}$ (range 19 – 23 h) was not dependent on the dose.

SAFETY

Single oral telmisartan doses of up to 320 mg, and single IV doses of up to 160 mg had no clinically significant effect on heart rate or blood pressure. All doses, whether administered orally or IV, were well tolerated. In healthy young subjects receiving single doses, there were no serious adverse events and no discontinuations occurred as a result of adverse events.

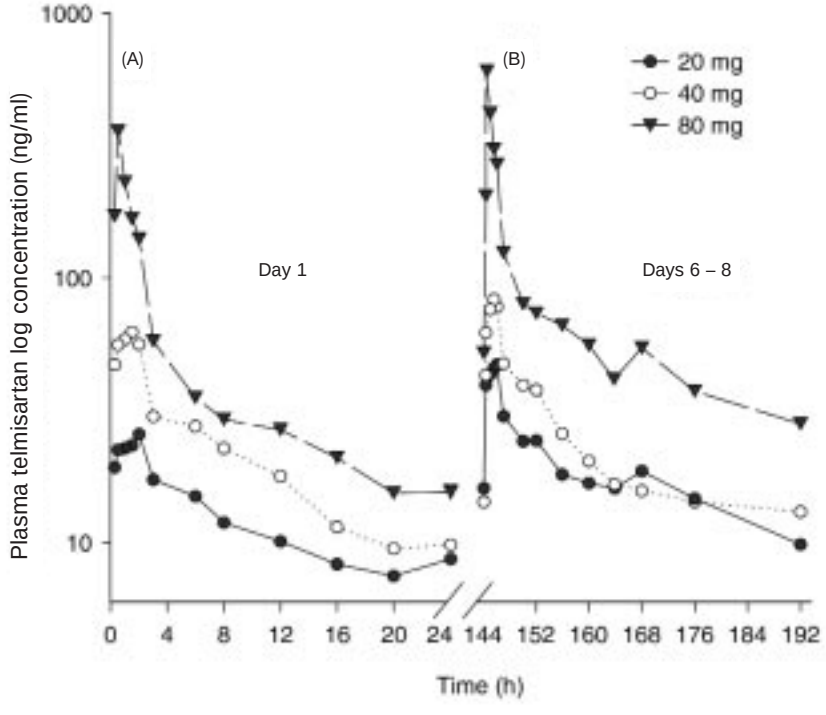
TABLE 4

Arithmetic means and percentage coefficient of variation of pharmacokinetic parameters of oral telmisartan given for 7 days in hypertensive patients

Parameter	10 mg (*n* = 6)	20 mg (*n* = 6)	40 mg (*n* = 6)	60 mg (*n* = 6)	80 mg (*n* = 6)	100 mg (*n* = 6)	120 mg (*n* = 6)	160 mg (*n* = 6)
C_{max} (ng/ml)	8.9; 44%	29.7; 47%	70.4; 45%	159; 33%	366; 50%	767; 56%	1131; 57%	1520; 47%
$C_{max,ss}$ (ng/ml)	12.9; 36%	46.3; 59%	88.2; 44%	328; 41%	601; 84%	1041; 27%	2017; 21%	2871; 85%
$AUC_{day\ 1}$ (ng · h/ml)	81.8; 52%	276; 42%	485; 47%	1249; 38%	1044; 38%	2284; 37%	2946; 26%	3177; 57
AUC_{ss} (ng · h/ml)	153; 47%	528; 56%	729; 47%	2556; 43%	2248; 81%	3403; 33%	5743; 41%	5357; 72
$t_{max,ss}$ (h)	2.0[a]	2.0[a]	1.5[a]	0.50[a]	0.50[a]	0.50[a]	0.50[a]	0.50[a]
R_A	2.0	1.8	1.5	2.0	2.0	1.5	1.9	1.6
$t_{1/2}$ (h)	25.2; 18%	27.8; 34%	36.9; 58%	55.3; 82%	26.8; 51%	43.1; 77%	23.1; 23%	18.4; 32%
MRT (h)	40.1; 8.5%	39.8; 30%	39.9; 53%	50.5; 60%	27.3; 30%	29.8; 76%	21.3; 39%	18.6; 27%
CL_{tot}/f (ml/min)	1307; 44%	918; 71%	1396; 101%	468; 49%	982; 84%	557; 46%	411; 47%	1148; 99%
V_z/f (l)	2956; 66%	2043; 66%	2589; 70%	2969; 118%	1779; 51%	1789; 55%	784; 41%	1817; 106%

[a]Median value.

FIGURE 2



Plasma concentration–time curves of telmisartan on (A) day 1 and (B) days 6 – 8 of treatment with 20, 40 and 80 mg administered orally once daily for 7 days to mild-to-moderate hypertensive subjects (n = 6).

Adverse events were predominantly mild to moderate in intensity, and there was no evidence of increases in the severity of adverse events with dose. There were no discontinuations of the trial.

There were five reports among the 33 healthy males receiving a single oral dose of telmisartan, and there were also eight such events when a single IV dose was administered to 44 healthy males. Headaches, occurring in six subjects, were the most frequent events considered to be related to study medication. However, reports of this adverse event were not confined to the subjects receiving telmisartan; headaches were also recorded in subjects receiving placebo. Occasional reports of syncope or dizziness, although possibly treatment-related, did not appear to be associated with reduced blood pressure. Increases in urine output were noted in healthy subjects receiving oral telmisartan at doses of 20, 40 and 160 mg.

The high plasma concentrations of telmisartan attained with multiple doses of 320 mg were also well tolerated. Although a significant increase ($P < 0.05$) in supine heart rate was noted, the values recorded were still within the physiological range.

Among the 14 normotensive elderly subjects evaluated for safety, there was a total

TABLE 5

Steady-state pharmacokinetics (geometric means ± percentage coefficient of variation) of telmisartan given orally for 28 days in hypertensive patients

Parameter	40 mg (*n* = 40)	80 mg (*n* = 41)	120 mg (*n* = 41)
C_{max} (ng/ml)	130; 73%	465; 125%	1046; 146%
t_{max} (h)	1.0[a]	1.0[a]	1.0[a]
$AUC_{0-\infty}$ (ng · h/ml)	1304; 81%	2651; 99%	4231; 91%
$t_{1/2}$ (h)	23.0; 47%	19.6; 45%	19.2; 52%
CL_{tot}/f (ml/min)	512; 82%	500; 100%	464; 91%

[a]Median value.

of 12 adverse events. Five of these events were considered to be probably related to study drug. The most frequent adverse event that was regarded as related to telmisartan was again headache. There was also a single report of a cough. In general, adverse events were classed as being mild or moderate in intensity. The two serious events were attributed to pre-existing disease and were unrelated to study drug.

Among the 169 mild-to-moderate hypertensive subjects treated with telmisartan in the two phase-II studies, the incidence and types of adverse events were similar to those recorded in the other healthy study groups. Again, there was no dose-related increase in either their incidence or intensity. The overall incidence of adverse events was 28.3% in the telmisartan 40-mg group, 25.5% in those receiving telmisartan 80 mg, and 36.2% in the telmisartan 120-mg group. By comparison, 40.7% of the 59 patients receiving placebo experienced one or more adverse event. In the hypertensive subjects, there was no evidence of first-dose effects, such as symptomatic orthostatic hypotension or excessive hypotension. Compared with the baseline ECG, no post-dosing changes were detected and there was no evidence of tachycardia. Overall, three serious events, all unrelated to telmisartan treatment, were recorded, with one fatality due to myocardial infarction.

No clinically significant changes in clinical laboratory parameters were identified in any of the three different populations studied.

DISCUSSION

In this series of studies involving normotensive young males, normotensive elderly males or females and mild-to-moderate hypertensive subjects, high systemic exposure to telmisartan was achieved. Maximum plasma concentrations of telmisartan were in the microgram range after both oral and IV dosing. Telmisartan has a high volume of distribution, indicating distribution into the tissue compartment. This pharmacokinetic characteristic, in conjunction with the high lipophilicity and membrane permeability,[25] contributes to effective AT_1 receptor blockade. Absolute bioavailability of at least 42%, rapid distribution of telmisartan after oral

administration, and the long $t_{1/2}$ of about 24 h support once-daily dosing without any risk of clinically relevant drug accumulation.

In all reported studies, which were conducted to establish the tolerability of telmisartan as well as to evaluate its pharmacokinetics, high intersubject variability of plasma concentrations was apparent. The single-dose studies in healthy subjects, because they were principally aimed at the assessment of telmisartan tolerability, involved the collection of only a limited number of plasma samples. These studies, therefore, did not allow an accurate assessment of telmisartan pharmacokinetic parameters (especially $t_{1/2}$), because of the limited number of data points in the terminal phase. The larger scale studies conducted in mild-to-moderate hypertensive subjects recorded a $t_{1/2}$ of > 20 h at steady state (range 17.6 – 42.2 h). Neutel and Smith,[19] in another study carried out in 228 patients with mild-to-moderate hypertension, found that the mean $t_{1/2}$ was approximately 24 h.

After IV infusion of telmisartan, C_{max} and $AUC_{0-\infty}$ displayed dose-proportional increases. By contrast, a more than proportional increase in C_{max} was detected with increasing oral doses. This effect, which was consistently observed in healthy young volunteers and elderly subjects, and in hypertensive patients, can be rationalized by saturable intestinal first-pass elimination of telmisartan by glucuronidation. With increasing doses, glucuronidation of the compound during absorption becomes saturated; hence, a greater fraction of the drug escapes first-pass elimination and thus enters the general circulation. This short-term saturation of first pass, which is probably caused by cofactor depletion in the enterocytes, contributes to the favourable absolute bioavailability of telmisartan and supports the generation of effective drug levels. This is confirmed by the observation that $t_{1/2}$ is not dose-dependent; the elimination of telmisartan follows linear kinetics.

A trend towards higher absolute bioavailability (57.4% and 57.5%, respectively) for 160-mg tablets and oral solution, compared with values of 42.4% and 47.3%, respectively, for the 40-mg tablet and 40-mg oral solution, was detected. The absolute bioavailability of telmisartan was also assessed in another study in which [^{14}C]telmisartan 40 mg was administered as a single oral or IV dose.[26] The primary purpose of that study was to characterize the mass balance/excretion of radioactivity. The plasma concentration–time data of the parent compound in that study indicated that the mean absolute bioavailability of orally administered telmisartan was 43%. The trend observed can also be explained by saturable first-pass elimination. At the higher dose, saturation of the pre-systemic elimination process (i.e. conjugation to glucuronic acid in the gut wall and/or liver) can lead to a greater fraction of the active drug reaching the systemic circulation.

The total clearance of telmisartan at all IV doses was in excess of 800 ml/min (range 802 – 944 ml/min), which is close to normal liver plasma flow (750 ml/min). A study using [^{14}C]telmisartan has shown that its elimination is almost exclusively via the liver, and only small amounts of glucuronic acid conjugates have been detected in urine.[26]

In vitro and *in vivo* studies have shown that telmisartan is highly bound to plasma protein (> 99.5 %), and that, in general, plasma protein binding remains unchanged over a range of telmisartan concentrations from 100 to 5000 ng/ml, which is equivalent to a dose of 320 mg. The fraction of telmisartan bound to plasma protein in

subjects with liver disease,[27] as well as in normotensive elderly subjects, is comparable to the protein-binding characteristics of telmisartan in healthy young volunteers. Although plasma protein binding of telmisartan is high, it is permissive (i.e. clearance and distribution are not restricted). The main binding protein is albumin, but others such as α-1-acid glycoprotein and lipoproteins also play a significant role. High protein binding of drugs is often regarded as a potential risk for protein displacement interactions. This, however, is not considered relevant for telmisartan because of the non-restrictive binding characteristics, due to high plasma clearance and the very high volume of distribution. This clearly indicates that the high degree of plasma protein binding does not restrict distribution and elimination of telmisartan. Upon displacement from binding proteins by competing drug molecules, free telmisartan will immediately undergo clearance and redistribution. As a result, there are only very transient, if any, increases in free plasma concentrations. The low specificity of binding and the very high capacity of albumin further minimizes the risk of clinically relevant plasma protein binding interactions. *In vivo* drug-interaction trials with highly protein-bound compounds (e.g. glibenclamide) showed no interaction (Boehringer Ingelheim, data on file). The non-restrictive character of telmisartan protein binding and, consequently, its high clearance and high volume of distribution differentiate telmisartan from other angiotensin II antagonists, such as candesartan cilexetil, valsartan, eprosartan, and the active metabolite of losartan.[23] The long elimination half-life also distinguishes telmisartan from other AT_1 receptor antagonists, which have shorter half-lives.[23]

Increasing age may be accompanied by changes in hepatic function, resulting in variations in the metabolism and elimination of drugs.[28 – 30] The plasma concentration–time profiles of telmisartan in elderly subjects resembled the profiles observed in younger subjects, and comparison of the pharmacokinetic parameters of telmisartan in the elderly with those observed in younger subjects at the 20 and 120 mg doses showed no significant differences. The results also show that there was no appreciable accumulation of telmisartan in elderly subjects. By contrast, variations in the pharmacokinetics of irbesartan have been noted in the elderly compared with younger subjects.[31]

During the study conducted in healthy elderly subjects, a trend was noted towards a variation in the pharmacokinetics in males and females. A possible explanation for the C_{max} and AUC being higher in elderly females than their male counterparts is that metabolic capacity of males is greater than that of females.[32] Thus, in men, a higher proportion of telmisartan is eliminated at its first pass through the liver. Any gender-related variations in the pharmacokinetic profile of telmisartan are unlikely to be of clinical significance, as the drug was extremely well tolerated by female subjects studied. There, therefore, appears to be no justification for dose adjustment according to gender.

The safety profile of telmisartan is good. The incidence of adverse events, which were generally non-specific in nature and mild in intensity, was low in normotensive patients of all ages, even at high single doses of 160 mg IV and multiple doses of 320 mg given orally. Similar incidences of events were detected in hypertensive patients treated for periods of up to 28 days. In common with other antihypertensive therapies,[33] headache was the most frequently reported adverse event related to

telmisartan treatment. There were no clinically significant changes in vital signs and clinical laboratory tests following treatment in any of the study populations evaluated.

Based on the findings of these studies, we conclude that therapeutic levels of telmisartan can be achieved using once-daily oral dosing and that the drug is well tolerated at a wide range of doses.

REFERENCES

1 Laragh JH: The renin system and new understanding of the complications of hypertension and their treatment. *Arzneimittelforschung* 1993; **43:** 247 – 254.

2 Jeunemaitre X, Soubrier F, Kotelevtsev YV, *et al*: Molecular basis of human hypertension: role of angiotensinogen. *Cell* 1992; **71:** 169 – 180.

3 Hall JE: Control of sodium excretion by angiotensin II: intrarenal mechanisms and blood pressure regulation. *Am J Physiol* 1986; **250** (6 Pt 2): R960 – R972.

4 Timmermans PBWM, Smith RD: Angiotensin II receptor subtypes: selective antagonists and functional correlates. *Eur Heart J* 1994; **15** (Suppl D): 79 – 87.

5 Gavras I, Gavras H: Angiotensin II – possible adverse effects on arteries, heart, brain, and kidney: experimental, clinical, and epidemiological evidence. In: *The Renin–Angiotensin System, I. Biochemistry/Physiology* (Robertson JIS, Nicholls MG, eds). London: Gower Medical Publishing, 1993; pp40.1 – 40.11.

6 Johnston CL, Arnolda L, Hiwatari M: Angiotensin-converting enzyme inhibitors in the treatment of hypertension. *Drugs* 1984; **27:** 271 – 277.

7 Urata H, Nishimura H, Ganten D, *et al*: Angiotensin-converting enzyme-independent pathways of angiotensin II formation in human tissues and cardiovascular diseases. *Blood Press* 1996; **2** (Suppl 2): 22 – 28.

8 Fuller RW, Dixon CM, Cuss FMC, *et al*: Bradykinin-induced bronchoconstriction in humans. Mode of action. *Am Rev Respir Dis* 1987; **135:** 176 – 180.

9 McEwan JR, Choudry NB, Fuller RW: The effect of sulindac on the abnormal cough reflex associated with dry cough. *J Pharmacol Exp Ther* 1990; **255:** 161 – 164.

10 McEwan JR, Choudry N, Street R, *et al*: Change in cough reflex after treatment with enalapril and ramipril. *BMJ* 1989; **299:** 13 – 16.

11 Just PM: The positive association of cough with angiotensin-converting enzyme inhibitors. *Pharmacotherapy* 1989; **9:** 82 – 87.

12 Oliverio MI, Coffman TM: Angiotensin-II receptors: new targets for anti-hypertensive therapy. *Clin Cardiol* 1997; **20:** 3 – 6.

13 Wienen W, Hauel N, Van Meel JC, *et al*: Pharmacological characterization of the novel nonpeptide angiotensin II receptor antagonist, BIBR 277. *Br J Pharmacol* 1993; **110:** 245 – 252.

14 Lacourcière Y: The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. *Int J Clin Pract* 1999; **53:** 99 – 103.

15 Lacourcière Y, Lenis J, Orchard R, *et al*: A comparison of the efficacies and duration of action of the angiotensin II receptor blockers telmisartan and

amlodipine. *Blood Press Monit* 1998; **3:** 295 – 302.

16 Mallion J, Siche J, Lacourcière Y, Telmisartan Blood Pressure Monitoring Group: ABPM comparison of the antihypertensive profiles of the selective angiotensin II receptor antagonists telmisartan and losartan in patients with mild-to-moderate hypertension. *J Human Hypertens* 1999; **13:** 657 – 664.

17 Lacourcière Y, Jacques L, Orchard R, *et al*: Placebo-controlled, multicenter comparison of 36-hour blood pressure control in ambulatory hypertensives with telmisartan and losartan (Abstract). *Can J Cardiol* 1998; **14:** 484.

18 Neutel JM, Smith DHG, Reilly PA: The efficacy and safety of telmisartan compared to enalapril in patients with severe hypertension. *Int J Clin Pract* 1999; **53:** 175 – 178.

19 Neutel JM, Smith DHG: Dose response and antihypertensive efficacy of the AT_1 receptor antagonist telmisartan in patients with mild to moderate hypertension. *Adv Ther* 1998; **15:** 206 – 217.

20 Smith DHG, Neutel JM, Morgenstern P: Once-daily telmisartan compared with enalapril in the treatment of hypertension. *Adv Ther* 1998; **15:** 229 – 240.

21 Karlberg BE, Lins L-E, Hermansson K, TEES Study Group: Efficacy and safety of telmisartan, a selective AT_1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. *J Hypertens* 1999; **17:** 293 – 302.

22 Neutel JM, Frishman WH, Oparil S, *et al*: Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertensiom. *Am J Ther* 1999; **6:** 161 – 166.

23 Csajka C, Buclin T, Brunner HR, *et al*: Pharmacokinetic–pharmacodynamic profile of angiotensin II receptor antagonists. *Clin Pharmacokinet* 1997; **32:** 1 – 29.

24 Ries UJ, Mihm G, Narr B, *et al*: 6-Substituted benzimidazoles as new nonpeptide angiotensin II receptor antagonists: synthesis, biological activity, and structure-activity relationships. *J Med Chem* 1993; **36:** 4040 – 4051.

25 Hauel NH, Ries UJ, Nar H, *et al*: Chemistry of telmisartan, a highly lipophilic angiotensin II antagonist with a long duration of action (Poster). *1st International Symposium on Angiotensin II Antagonism*, London, UK, 1997.

26 Stangier J, Schmid J, Türck D, *et al*: Absorption, metabolism, and excretion of intravenously and orally administered [^{14}C]telmisartan in healthy volunteers. *J Clin Pharmacol* 2000 (in press).

27 Stangier J, Su CAPF, Schöndorfer G, *et al*: Pharmacokinetics and safety of intravenous and oral telmisartan 20 mg and 120 mg in subjects with hepatic impairment compared with healthy volunteers. *J Clin Pharmacol* 2000 (in press).

28 Woodhouse K, Wynne HA: Age-related changes in hepatic function. Implications for drug therapy. *Drugs Aging* 1992; **2:** 243 – 255.

29 Le Couteur DG, McLean AJ: The aging liver: drug clearance and an oxygen diffusion barrier hypothesis. *Clin Pharmacokinet* 1998; **34:** 359 – 373.

30 Woodhouse K: Drugs and the liver. Part III: Aging of the liver and the metabolism of drugs. *Biopharm Drug Dispos* 1992; **13:** 311 – 320.

31 Vachharajani NN, Shyu WC, Smith RA, *et al*: The effects of age and gender on the pharmacokinetics of irbesartan. *Br J*

Clin Pharmacol 1998; **46:** 611 – 613.

32 Harris RZ, Benet LZ, Schwartz JB: Gender effects in pharmacokinetics and pharmacodynamics. *Drugs* 1995; **50:** 222 – 239.

33 Lindholm LH: Assessing the safety profile of a new antihypertensive agent. *J Hypertens* 1995; **13** (Suppl 4): S5 – S9.

J Stangier, CAPF Su and W Roth
Pharmacokinetics of Orally and Intravenously Administered Telmisartan in Healthy Young and Elderly Volunteers and in Hypertensive Patients
The Journal of International Medical Research
2000; **28:** 149 – 167
Received for publication 27 June 2000
Accepted 30 June 2000

Address for correspondence
Dr J Stangier
Department of Pharmacokinetics and Drug Metabolism, Boehringer Ingelheim Pharma KG, Birkendorfer Strasse, D-88397 Biberach an der Riss, Germany.