Single dose and steady state pharmacokinetics of temocapril and temocaprilat in young and elderly hypertensive patients

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Aims The aim of this study was to determine the potential impact of age on the pharmacokinetics of temocapril and its pharmacologically active diacid metabolite, temocaprilat, in hypertensive patients.

Methods Male and female patients with mild to moderate essential hypertension (DBP 95–114 mmHg inclusive) were allocated to two age groups: young, ≤ 40 years; elderly, ≥ 69 years, ($n = 18$ per group). In Part I of the study, subjects took a single oral tablet dose of 20 mg temocapril hydrochloride following an overnight fast. In Part II they took seven once daily oral tablet doses of 20 mg temocapril hydrochloride. Pharmacokinetic profiles were determined after the single and the last dose. Trough plasma samples were taken before each dose in Part II. Urine was collected for 24 h following the single and the last dose.

Results Steady state was reached within 1 week in both groups. Statistically significant differences were detected in AUC and AUC_{ss} for temocaprilat as well as in CL_R for temocapril and temocaprilat, respectively, after a single dose and at steady state. All other pharmacokinetic parameters for temocapril and temocaprilat did not show any significant difference.

Conclusions The pharmacokinetic differences detected in the elderly do not require a dose adjustment *per se*. Nonetheless, a lower starting dose may be appropriate as elderly hypertensive patients are usually considered to be at an increased risk of first dose hypotension at the onset of treatment with an ACE inhibitor.

Keywords: ACE inhibitor, elderly, hypertension, pharmacokinetics, temocapril, temocaprilat

Introduction

Inhibitors of the angiotensin converting enzyme (ACE) are of paramount importance for the treatment of various cardiovascular disorders. Besides their blood pressure-lowering effect in hypertensive patients [1], ACE inhibitors have been shown to prolong life in patients with congestive heart failure [2] and post myocardial infarction [3]. Moreover, several studies indicate beneficial effects of this class of drugs for preserving renal function in patients with diabetic [4–6] and nondiabetic nephropathy [7].

With the exception of captopril [8] and lisinopril [9], ACE inhibitors are administered as prodrugs which require bioactivation by nonspecific esterases [10]. Thus, pharmacokinetic evaluation of prodrug-type ACE inhibitors has to focus on the disposition of both the parent compound as the source of the pharmacologically active metabolite and the active metabolite itself.

Temocapril (INN) hydrochloride, (+)–[(2S,6R)–6-[(S)–1-(ethoxycarbonyl)–3-phenyl-propyl] amino]–5-oxo–2-(2-thienyl)–1,4-thiazepan–4-yl] acetic acid monohydrochloride, is an orally active, long-acting prodrug-type ACE inhibitor with a dual excretion pathway. It is rapidly absorbed and converted exclusively to its pharmacologically

active diacid metabolite, temocaprilat, predominantly by esterases of the liver and, to a minor extent, also by esterases of the gut mucosa. Dose linearity was demonstrated for temocaprilat over the dose range of 5–40 mg once daily [Sankyo, data on file].

In this study, we investigated the pharmacokinetics of temocapril and temocaprilat after a single oral tablet dose and after seven once daily doses of 20 mg temocapril hydrochloride in one target population for ACE inhibitors, namely young (≤ 40 years) and elderly (usually ≥ 65 years) hypertensive patients. The study design, a single dose administration followed by multiple doses supposed to result in steady state conditions, is the most suitable way to get the full range of information on the disposition of a prodrug-type ACE inhibitor. The dose studied, 20 mg, was selected as it is an effective dose with respect to blood pressure lowering [11]. As the population of hypertensive patients consists of more and more elderly and very elderly (usually ≥ 75 years), a particular emphasis was laid on the potential influence of age on the pharmacokinetics of this drug.

Methods

Subjects and study design

This single-centre open-label trial was conducted in accordance with the provisions of the German Medicines Act, the

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EC Note for Guidance on Good Clinical Practice and the Declaration of Helsinki. The trial protocol was approved by an independent ethics committee. All 36 Caucasian patients with mild to moderate hypertension (diastolic blood pressure 95–114 mmHg inclusive) provided written informed consent to participate. They were allocated to two age groups: young, ≤ 40 years; elderly, ≥ 69 years, ($n=18$ per group). Patient characteristics are summarized in Table 1. Haematology and standard biochemistry baseline results were to be within the normal range or deviations to be without clinical significance, i.e. serum ALAT and/or ASAT below twice the upper limit of normal, serum bilirubin up to 1.5 times the upper limit of normal. Mean baseline creatinine clearance was calculated according to Cockcroft & Gault [12] using a factor of 0.85 in female patients. As the cytochrome P450 enzymes, in particular the CYP1A family, are not involved in the metabolism of temocapril, both smokers and nonsmokers were included in the study (Table 1). Any antihypertensive treatment was tapered off during the 3 week screening phase prior to the first administration of the study drug.

Part I Both groups received a single oral 20 mg temocapril hydrochloride tablet (manufacturer: SANKYO PHARMA GmbH, Munich, Germany) administered under supervision with 150 ml water following an overnight fast. Food was allowed 2 h post dose.

Part II A steady-state trial, conducted after a 6 day washout period, involving 7 days dosing of a 20 mg temocapril hydrochloride tablet once daily as described above. Trough blood samples were taken before each dose.

Table 1 Patient characteristics ($n=18$ in each group).

	Young	Elderly
Sex: males/females	11/7	6/12
Age (years)		
Mean	33.6	74.0
Range	24–40	69–83
Weight (kg)		
Mean	78.8	71.6
Range	52–111	54–93
Height (cm)		
Mean	173.9	162.9
Range	154–193	152–174
Smokers/nonsmokers	9/9	6/12
CL _{CR} (ml min ⁻¹)		
Median	103.9*	58.7*
Range	77.3–147.9	37.2–81.6

CL_{CR} Creatinine clearance at baseline calculated according to the equation of Cockcroft & Gault [12]:

$$CL_{CR} = \frac{[140 - \text{age (years)}] \cdot \text{bodyweight (kg)}}{\text{serum creatinine (mg 100 ml}^{-1}\text{)} \cdot 72} \quad \text{for male subjects, and}$$

85% of this value for female subjects.

*Statistically significant difference between young and elderly group (Wilcoxon rank sum test, $P < 0.05$).

Sample collection and assays

After the first dose, blood samples were taken at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120 and 144 h postdose. After the last dose, blood samples were taken at the same time points up to 96 h postdose. Blood was drawn into heparinised tubes and kept on ice prior to centrifugation at 4 °C and 3000 rev min⁻¹ for 10 min. Total urine output was collected for 24 h following the first and last dose. Plasma and urine samples were stored at -20 °C until analysis. Plasma and urine concentrations of temocapril and temocaprilat were determined using capillary gas chromatography-negative ion chemical ionization mass spectrometry (GC-MS) [13]. A deuterated analogue was used as internal standard and all three compounds were extracted from plasma and urine using a two-stage solid phase procedure with Sep-Pak C₁₈ and Sep-Pak silica cartridges. Sequential derivatization of carboxylic acid and secondary amino groups was carried out using diazomethane and trifluoroacetic acid anhydride, respectively. Negative ion chemical ionization of the derivatives using methane as reagent gas produced intense high mass fragments ideal for selected ion monitoring. The combination of capillary gas chromatography, derivatization and monitoring of specific high mass negative ions ensured no interference from coextracted endogenous plasma components. Imprecision of the assay ranged from 4.6% to 6.6% for temocapril and from 5.0% to 9.2% for temocaprilat in plasma. In urine, the assay imprecision did not exceed 14.1% and 6.4% for temocapril and its diacid, respectively. Inaccuracy of the mean data ranged from -2.7% to +2.1% (temocapril) and from -0.6% to +2.7% (temocaprilat) in plasma quality control (QC) samples. Individual urine QC sample results showed maximum percentage errors of -11.0% and -19.8% for temocapril and its diacid, respectively. The lower limit of quantification (LOQ) was 0.50 ng ml⁻¹ for both analytes in plasma and urine.

Pharmacokinetic evaluation and statistical analysis

Pharmacokinetic data were analysed by noncompartmental techniques using the TopFit 2.0 software. For peak concentration in plasma, C_{max} , and time to reach peak concentration, t_{max} , observed values were taken. The apparent terminal rate constant, λ_z , was determined by linear regression of the terminal phase of the logarithmic plasma concentration *vs* time curve. The terminal phase was assessed subjectively over the final three to five sampling points with a measured concentration equal or above the LLQ. The terminal half-life, $t_{1/2}$, was calculated as $(\ln 2)/\lambda_z$. After single dosing, the area under the plasma concentration *vs* time curve (AUC) was calculated by the linear-logarithmic trapezoidal rule up to the last time at which the concentration was equal to or above the LOQ, AUC_t , and extrapolated to infinity by dividing the plasma concentration at time t by λ_z and adding this value to AUC_t . After multiple dosing, the AUC during the dosing interval ($\tau=24$ h) at steady state (SS), AUC_{ss} , was calculated by the linear-logarithmic trapezoidal rule up to 24 h after the last dose. The apparent total clearance from plasma after oral administration, CL/F , was calculated by dividing the dose (20 mg) by AUC and

AUC_{ss} for temocapril, respectively. Renal clearance from plasma, CL_R , was calculated by dividing urinary recovery of temocapril, Ae_{24} , and temocaprilat, $Ae(m)_{24}$, by the related AUC_{24} and AUC_{ss} , respectively. During Part II, the temocapril and temocaprilat trough plasma concentrations after 5, 6 and 7 days of dosing were analysed by regression analysis. Steady state was characterized by a slope not significantly different from zero. SAS version 6.03 was used for all statistical analyses.

Results

Patients characteristics are summarized in Table 1. There was a statistically significant difference in median (range) baseline creatinine clearance (Cockcroft & Gault) between young and elderly patients, i.e. 103.9 (77.3–147.9) and 58.7 (37.2–81.6) $ml\ min^{-1}$, respectively (Table 1).

The mean (s.d.) plasma concentration *vs* time curves of temocapril and temocaprilat after seven daily oral doses of 20 mg temocapril hydrochloride are shown in Figure 1a and b.

Trough plasma concentrations of temocapril were always below the LOQ. Trough plasma levels of temocaprilat increased from day to day when compared with the 24 h value after a single dose. After 5, 6 and 7 days of dosing they did not increase any more, i.e. linear regression analysis

did not reveal a slope significantly different from zero. Thus, steady state was reached within 1 week.

Pharmacokinetic parameters of temocapril and temocaprilat are displayed in Tables 2a and b. Temocapril was rapidly absorbed with median t_{max} of 1 h after single and multiple doses in both groups. Temocaprilat also appeared rapidly in plasma with median t_{max} of 1.5 h after dosing. No statistically significant differences between the young and elderly groups were detected in any pharmacokinetic parameter for temocapril with the exception of renal clearance or in C_{max} , t_{max} and $t_{1/2}$ for temocaprilat after a single dose and at steady state, respectively. In contrast, statistically significant differences were detected in AUC and AUC_{ss} for temocaprilat after a single dose [geometric mean AUC (geometric coefficient of variation, geometric CV), young: 3802 (3.4%); elderly: 5699 (3.6%) $ng\ ml^{-1}\ h$] and at steady state [AUC_{ss} , young: 3457 (2.7%); elderly: 4712 (4.1%) $ng\ ml^{-1}\ h$] and in CL_R for temocapril and temocaprilat, respectively, after a single dose [geometric mean (geometric CV), temocapril, young: 45.8 (18.6%); elderly: 18.2 (19.0%) $ml\ min^{-1}$; temocaprilat, young 20.5 (11.2%); elderly: 12.6 (11.0%) $ml\ min^{-1}$] and at steady state [temocapril, young: 45.9 (20.9%); elderly: 17.4 (22.4%) $ml\ min^{-1}$; temocaprilat, young 22.5 (13.1%); elderly: 14.7 (10.6%) $ml\ min^{-1}$] (Tables 2a and b). The 95% confidence intervals (CI) for the ratio (elderly/young) of the geometric means further illustrate the statistically significant differences, i.e. if 1.0 is not included in the 95% CI, there was a significant difference between the groups with $P < 0.05$ (Tables 2a and b).

After the last dose, a 78-year-old male patient experienced a severe angioedema involving the larynx. The relationship to temocapril was considered highly probable by the investigator. The patient fully recovered after i.v. administration of clemastine and prednisolone. This patient was not known to have any previous event of angioedema or any other drug intolerance and subsequently returned to his former ACE inhibitor, captopril, without repercussions. Furthermore, one young patient with a history of migraine-like symptoms reported moderate headache and eight young and four elderly patients reported mild headache. The investigator predominantly considered the events of headache unrelated to temocapril treatment. Two young patients suffered from mild coughing possibly related to study drug.

Discussion

In young and elderly hypertensive patients, temocapril was absorbed rapidly and readily metabolised to its active diacid metabolite, temocaprilat. Steady state was reached within 1 week in both groups. No statistically significant differences between the young and elderly groups were detected in any pharmacokinetic parameter for temocapril or in C_{max} , t_{max} and $t_{1/2}$ for temocaprilat after a single dose and at steady state. In contrast, statistically significant differences were detected in AUC and AUC_{ss} for temocaprilat as well as in CL_R for temocapril and temocaprilat, respectively, after a single dose and at steady state.

In another study, absolute bioavailability of temocaprilat after oral administration of temocapril hydrochloride was about 65% in young male and female subjects. About 57%

Figure 1 Mean (s.d.) plasma concentration *vs* time curves of (a) temocapril and (b) temocaprilat after seven once daily oral doses of 20 mg temocapril hydrochloride in young and elderly hypertensive patients

○ Young hypertensive patients (≤ 40 years of age); $n = 18$
 □ Elderly hypertensive patients (≥ 69 years of age); $n = 18$

Table 2a Pharmacokinetic parameters of (a) temocapril and (b) temocaprilat after a single oral dose of 20 mg temocapril hydrochloride and after seven once daily oral doses of 20 mg temocapril hydrochloride, i.e. at steady state ($n=18$ hypertensive patients in each group). Values are geometric means (geometric CV) except $t_{\max}$ which is median (range). Also shown are 95% CI for the ratio elderly/young of the geometric Means.

		Single dose		Steady state	
$C_{\max}$ (ng ml ⁻¹)	Young	136 (14.0%)	[0.88–2.04]	139 (12.1%)	[0.88–1.91]
	Elderly	181 (10.5%)		180 (10.6%)	
$t_{\max}$ (h)	Young	1.0 (0.5–2.0)	[0.92–1.81]	1.0 (0.5–2.5)	[0.97–1.88]
	Elderly	1.0 (0.5–2.0)		1.0 (0.5–2.0)	
AUC and AUC _{ss} (ng ml ⁻¹ h)	Young	141 (9.4%)	[0.67–1.53]	140 (8.1%)	[0.61–1.77]
	Elderly	182 (10.3%)		189 (10.9%)	
$t_{1/2}$ (h)	Young	1.5 (161%)	[0.55–1.09]	1.6 (159%)	[0.53–1.04]
	Elderly	1.5 (154%)		1.7 (150%)	
CL/F (ml min ⁻¹)	Young	2204 (6.0%)	[0.26–0.61]	2206 (5.5%)	[0.23–0.62]
	Elderly	1705 (7.2%)		1636 (7.7%)	
CL _R (ml min ⁻¹)	Young	45.8 (18.6%)*	[0.26–0.61]	45.9 (20.9%)*	[0.23–0.62]
	Elderly	18.2 (19.0%)*		17.4 (22.4%)*	

Table 2b

		Single dose		Steady state	
$C_{\max}$ (ng ml ⁻¹)	Young	760 (3.9%)	[0.95–1.36]	828 (3.5%)	[0.89–1.32]
	Elderly	863 (4.0%)		893(5.0%)	
$t_{\max}$ (h)	Young	1.5 (1.0–3.0)	[1.23–1.83]	1.5 (1.0–2.5)	[1.12–1.66]
	Elderly	1.5 (1.0–2.5)		1.5 (1.0–3.0)	
AUC and AUC _{ss} (ng ml ⁻¹ h)	Young	3802 (3.4%)*	[0.71–1.11]	3457 (2.7%)*	[0.81–1.53]
	Elderly	5699 (3.6%)*		4712 (4.1%)*	
$t_{1/2}$ (h)	Young	26.9 (13.0%)	[0.50–0.76]	19.4 (15.9%)	[0.51–0.83]
	Elderly	23.8 (6.0%)		21.6(15.0%)	
CL _R (ml min ⁻¹)	Young	20.5 (11.2%)*	[0.50–0.76]	22.5 (13.1%)*	[0.51–0.83]
	Elderly	12.6 (11.0%)*		14.7 (10.6%)*	

AUC Area under the plasma concentration-time curve to infinite time after a single oral dose of 20 mg temocapril hydrochloride;

AUC_{ss} Area under the plasma concentration-time curve during the dosing interval ($\tau=24$ h) after seven once daily oral doses of 20 mg temocapril hydrochloride.

*Statistically significant difference between young and elderly group (Wilcoxon rank sum test, $P<0.05$).

of an intravenously administered dose of temocaprilat were excreted in urine [Sankyo, data on file]. This amount corresponds to about 37% (57% out of 65%) urinary recovery of temocaprilat after an orally administered dose of temocapril.

The disposition of temocapril and temocaprilat in renal impairment has been studied after a single dose [14] and at steady state [15]. In 32 Caucasian hypertensive patients with varying degrees of renal impairment, 14 once daily oral tablet doses of 10 mg temocapril hydrochloride were administered. A statistically significant decrease in CL_R for temocapril and temocaprilat with decreasing renal function was detected. AUC_{ss} for temocaprilat increased and $t_{1/2}$ for temocaprilat was prolonged. However, the changes in AUC_{ss} and $t_{1/2}$ did not parallel the decrease in CL_R for temocaprilat

suggesting a compensatory excretion pathway for temocaprilat [15].

Biliary excretion of temocapril and temocaprilat was demonstrated in humans [16]. Moreover, in another study, a single oral tablet dose of temocapril hydrochloride was administered to 12 patients undergoing endoscopic retrograde cholangio-pancreatography [Sankyo, data on file]. Temocapril and temocaprilat were detected in bile sampled directly from the common bile duct. Thus, there was evidence for a dual route of excretion for both temocapril and its diacid. Recently, it was demonstrated that the ATP-dependent canalicular multispecific organic anion transporter is handling the biliary excretion of temocaprilat in rats [17].

Although the change in renal clearance for temocapril was statistically significant, no significant difference in AUC

for temocapril was detected. As for temocaprilat, it is unlikely that the significant change in renal clearance alone has accounted for the changes in AUC because of the balanced renal and biliary excretion of temocaprilat. It is not possible from this study to determine what factors had been responsible, although age-related changes in hepatic and biliary function may be involved.

The absence of a specific age-dependent difference in the pharmacokinetics of other ACE inhibitors, e.g. benazepril [18], cilazapril [19] and fosinopril [20], was shown, whereas an age-dependent change in the pharmacokinetics of enalaprilat was demonstrated [21].

Temocapril was in general well tolerated and was associated with a low incidence of adverse events in both young and elderly patients.

In conclusion, the differences detected in AUC and AUC_{ss} for temocaprilat as well as in CL_R for temocapril and temocaprilat were of such an order that dose reductions of temocapril hydrochloride in the elderly are not considered necessary in the absence of moderate to severe renal impairment. Nonetheless, a lower starting dose in elderly hypertensive patients may be appropriate as those patients are usually considered to be at an increased risk of first dose hypotension at the onset of treatment with an ACE inhibitor.

This study was supported by a grant of Sankyo Europe GmbH, Duesseldorf, Germany.

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(Received 11 November 1997,
accepted 20 April 1998)