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PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetics and safety of candesartan cilexetil in subjects with normal and impaired liver function

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Abstract *Objective*: The influence of liver disease on the pharmacokinetics of candesartan, a long-acting selective AT_1 subtype angiotensin II receptor antagonist was studied.
Methods: Twelve healthy subjects and 12 patients with mild to moderate liver impairment received a single oral dose of 12 mg of candesartan cilexetil on day 1 and once-daily doses of 12 mg on days 3–7. The drug was taken before breakfast. Serial blood samples were collected for 48 h after the first and last administration on days 1 and 7. Serum was analyzed for unchanged candesartan by HPLC with UV detection.
Results: The pharmacokinetic parameters on days 1 and 7 revealed no statistically significant influence of liver impairment on the pharmacokinetics of candesartan. Following single dose administration on day 1, the mean C_{max} was 95.2 ng · ml^{-1} in healthy subjects and 109 ng · ml^{-1} in the patients. The $AUC_{0-\infty}$ was 909 ng.h · ml^{-1} in healthy volunteers and 1107 ng.h · ml^{-1} in patients and the elimination half-life was 9.3 h in healthy volunteers and 12 h in the patients. At steady state on day 7, mean C_{max} values were similar in both groups (112 vs 116 ng · ml^{-1}); the AUC_{τ} was 880 ng.h · ml^{-1} in healthy subjects and 1080 ng.h · ml^{-1} in patients while the elimination half-life was 10 h in healthy subjects and 12 h in the patients with liver impairment. The $AUC_{0-\infty}$ on day 1 was almost identical to the AUC_{τ} on day 7. A moderate drug accumulation of 20%, which does not require a dose adjustment, was observed following once-daily dosing in both groups. No serious or severe adverse events were reported.
Conclusion: Mild to moderate liver impairment has no clinically relevant effect on candesartan pharmacokinetics, and no dose adjustment is required for such patients.

Key words Candesartan, Hepatic impairment

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Introduction

The angiotensin II (AT_1) receptor antagonists represent a new class of cardiovascular drug within the group of antihypertensive compounds with different biological actions [1]. In comparison with established ACE inhibitors, angiotensin II AT_1 receptor antagonists are more specific in their mode of action. Since angiotensin II is the primary effector of the renin-angiotensin system, angiotensin II AT_1 receptor antagonists are likely to lower the blood pressure by minimal and selective intervention in the endogenous system. Common adverse effects of ACE inhibitors such as dry cough and angioedema may be avoided [2].

Candesartan is a new long-acting angiotensin II type 1 receptor antagonist. It is administered orally as a prodrug, candesartan cilexetil, which is completely hydrolyzed to the active compound during absorption. Initial studies in healthy subjects and patients with mild to moderate hypertension show that candesartan cilexetil provides sustained angiotensin II antagonistic and antihypertensive activity for at least 24 h after a dose, and that it is well tolerated [3, 4].

Candesartan is mainly excreted unchanged through renal and biliary routes [5]. However, since some 20–30% is metabolized in the liver by de-ethylation and glucuronidation to inactive metabolites, decreased liver function could alter the pharmacokinetics of candesar-

tan. The present study was designed to compare the pharmacokinetics of candesartan in normotensive patients with mild to moderate liver impairment and healthy subjects after single and repeated doses.

Materials and methods

Clinical part

Written informed consent was obtained and the protocol was approved by the Ethics Committee of the Medical Faculty of the University of Dresden, Germany. Twelve Healthy subjects and 13 patients with impaired liver function were studied. One patient withdrew on day 3 and was excluded from the analysis. The demographic data are given in Table 1.

Patients with impaired liver function and healthy volunteers were matched for age, height, weight and sex as far as possible. A diagnosis of mild to moderate chronic liver dysfunction was based on transaminase activities, antipyrine clearance [6], ultrasound and in two cases by liver biopsy. Subjects with an antipyrine clearance between 10 ml · min^{-1} and 35 ml · min^{-1} were assigned to the liver disease group. Fatty liver was confirmed by ultrasound in all 12 patients. Patients with liver cirrhosis, chronic active hepatitis and cirrhosis with portocaval shunts were not included. The liver function tests at baseline are shown in Table 1. Patients with severe cardiac disease or hypertension were excluded.

In the morning of day 1 and days 3–7, one tablet of candesartan cilexetil 12 mg was taken under supervision with 100 ml of tap water. Breakfast was served immediately after drug intake.

Blood was sampled before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36 h and 48 h following candesartan cilexetil administration on days 1 and 7. In addition, trough samples were taken pre-dose on study days 3, 5, and 6.

Serum was stored at −20 °C. For determination of the free fraction of candesartan in serum (f_u), samples from each subject were pooled on study day 1 and day 7.

Assay

Serum was analyzed for candesartan by high-*p*erformance *l*iquid *c*hromatography (HPLC) with UV-detection at 210 nm [7]. The lower limit of quantification was 2.0 ng · ml^{-1}, and the limit of detection was 1.0 ng · ml^{-1}. The coefficient of variation for quality control samples ranged between 7.1% and 11.6%.

Protein binding was determined by ultrafiltration (Amicon Centrifree Grace B.V., Cpelle, The Netherlands) and subsequent scintillation counting. ^{14}C-labelled candesartan was added to pooled serum samples of each subject and the free fraction (f_u) was derived from the radioactivity ratio (ultrafiltrate/serum) and total candesartan concentration (free + protein bound). The coefficient of variation of the ^{14}C-labelled samples was 1.7% for serum and 20.2% for filtrate.

Pharmacokinetic evaluation

Pharmacokinetic parameters were evaluated by non-compartmental analysis [8].

Day 1 (single dose)

Peak serum concentration (C_{max}) and the corresponding time to reach the peak concentration (t_{max}) was taken directly from the observed data. AUC_τ, the area under the concentration-time curve, was calculated up to the actual time of 24 h after dosing, where τ is the dosing interval. The AUC_{0-t} was extrapolated to infinity ($AUC_{0-\infty}$) using the following formula:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{t_{1/2} \cdot C_{last}}{\ln(2)}$$

Day 7 (multiple dose at steady state)

The accumulation factor R was calculated as:

$$R = AUC_t \text{ (day 7)} / AUC_\tau \text{ (day 1)}$$

Table 1 Demographic data and liver function parameters of healthy subjects and patients with liver impairment. Values are given as means (range)

	Healthy volunteers (n = 12)	Patients with liver disease (n = 13)[a]
Demographic data		
Age (years)	46.3 (32–71)	51.5 (31–71)
Height (cm)	173 (165–180)	176 (164–191)
Weight (kg)	68.8 (59–85)	78.7 (59–99)
Race (Caucasian)	12	13
Sex (male/female)	7/5	9/4
Prothrombin time (%)	96.6 (84–100)	96.5 (82–100)
Blood pressure (mmHg)		
Systolic	128.1 (120–140)	133.5 (120–145)
Diastolic	81.5 (80–85)	81.6 (80–85)
Liver function tests		
SGOT (U · l^{-1})	8.8 (6.1–13.2) (5–17)[b]	26.6 (11.2–56.4)
SGPT (U · l^{-1})	9.7 (5.5–18.8) (5–23)[b]	36.3 (18.6–66.1)
γ–GT (U · l^{-1})	10.2 (3.3–17.2) (6–28)[b]	72.9 (14.7–239.8)
Antipyrine clearance (ml · min^{-1})	39.5 (35–60) (> 35)[b]	21.6 (10.2–31)

[a] Thirteen patients were enrolled; one was withdrawn from the study and not evaluated for pharmacokinetics
[b] Normal range given by investigator

If the pharmacokinetics are linear the AUC_τ on day 7 at steady state should equal the $AUC_{0-\infty}$ on day 1 and the ratio of these two areas "R_x" should approach 1:

$$R_x = AUC_\tau \text{ (day 7)}/AUC_{0-\infty} \text{ (day 1)} \cong 1$$

Safety evaluation

Pre-study screening included medical history, physical examination, blood pressure, pulse rate, ECG and clinical laboratory investigation including liver function tests. Within 1 week of the last drug administration, the physical examination, blood pressure, pulse rate, ECGs and routine laboratory tests were repeated. Adverse events were recorded during treatment (days 1–8) and at follow-up (days 9–14).

Statistical analysis

Mean, standard deviation, median and 95% confidence intervals were calculated following single dosing on day 1 and multiple dosing on day 7. An unpaired student *t*-test was performed to compare the kinetic data of patients and healthy volunteers on day 1 and day 7.

An additive pharmacokinetic model was assumed for $t_{½}$, C_{min} and t_{max} and therefore the calculation of mean, standard deviation and 95% confidence intervals was based on non-transformed data (normal distribution).

A multiplicative pharmacokinetic model was assumed for C_{max}, AUC_τ, $AUC_{0-\infty}$ and *R*, and therefore the calculation of mean, standard deviation and 95% confidence intervals was based on log-transformed data (log-normal distribution).

Results

Pharmacokinetics

The mean concentration vs time profile of candesartan obtained after a single oral dose of 12 mg candesartan cilexetil on day 1 was similar to that obtained at steady-state conditions on day 7 (Fig. 1). Pharmacokinetic parameters are summarized for days 1 and 7 in Table 2.

On day 1 the mean serum concentrations of candesartan the liver disease patients were slightly higher than in the healthy volunteers. In the patients, the mean C_{max} was approximately 14% higher than in healthy subjects (109 ng · ml^{-1} vs 95.2 ng · ml^{-1}) and the AUC values were increased by 22–24% ($AUC_{0-\infty}$ =

Table 2 Pharmacokinetic parameters of candesartan following single oral administration of 12 mg candesartan cilexetil on study day 1 and at steady state following multiple dosing of 12 mg once daily on study day 7 in patients with liver disease (n = 12) and healthy volunteers (n = 12). Values are presented as geometric means (SD), except for C_{min}, $t_{½}$ and t_{max} which are given as arithmetic means (SD) [medians]. C_{max} maximum concentration, C_{min} minimum concentration, t_{max} time to reach maximum concentration, $t_{½}$ elimination half-life, AUC_τ area under the plasma concentration time curve from 0–24 h, $AUC_{0-\infty}$ area under the plasma concentration time curve extrapolated to infinity; *R* accumulation factor AUC_τ (day 7)/AUC_τ (day 1)

	Healthy volunteers	Patients with liver disease
Study day 1		
$t_{½}$ (h)	9.3 (2.7) [9.4]	12 (5.3) [10.5]
C_{max} (ng · ml^{-1})	95.2 (29.9)	109 (40.1)
t_{max} (h)	3.0 (1.4) [2.5]	2.7 (0.55) [2.5]
AUC_τ (ng.h · ml^{-1})	708 (314)	881 (334)
$AUC_{0-\infty}$ (ng.h · ml^{-1})	909 (307)	1107 (560)
Study day 7		
$t_{½}$ (h)	10 (2.1) [10]	12 (4.2) [10]
C_{min} (ng · ml^{-1})	12.3 (5.12) [11.1]	15.2 (13.8) [14.1]
C_{max} (ng · ml^{-1})	116 (31.2)	112 (50.2)
t_{max} (h)	2.6 (0.36) [2.5]	2.8 (1.1) [2.5]
AUC_τ (ng.h · ml^{-1})	880 (205)	1080 (458)
R	1.24 (0.81)	1.21 (0.35)

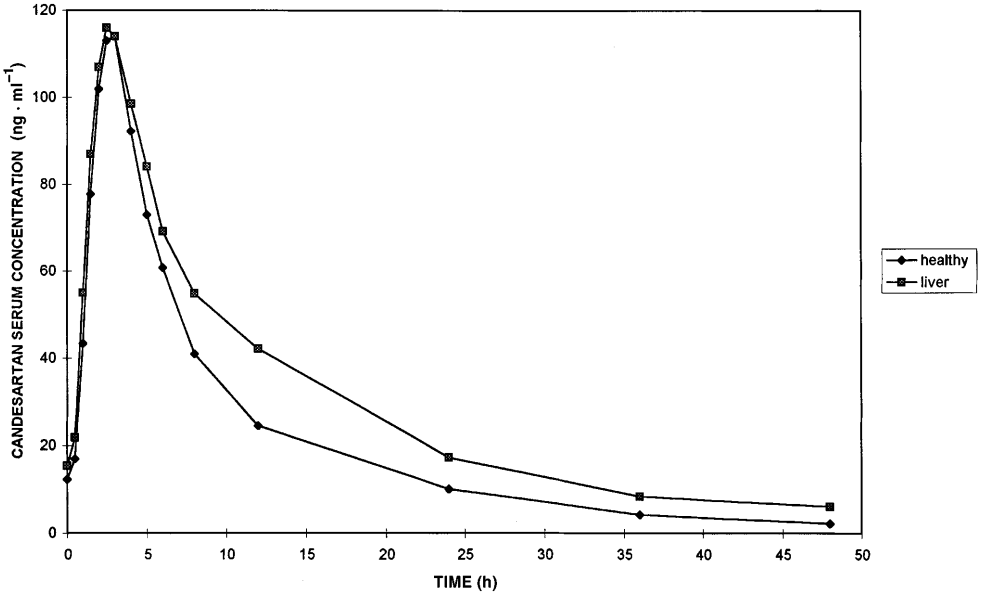

Fig. 1 Mean candesartan serum concentrations following multiple once-daily oral dosing of 12 mg candesartan cilexetil on study day 7 in 12 patients with liver disease (–□–) and in 12 healthy volunteers (–◇–)

1107 ng.h · ml^{-1} in patients and 909 ng.h · ml^{-1} in healthy subjects; AUC_τ = 881 ng.h · ml^{-1} in patients and 708 ng.h · ml^{-1} in healthy subjects); in addition, the elimination half-life was prolonged by 29% (12 h in patients vs 9.3 h in healthy volunteers; Table 2).

On day 7, when steady-state conditions were reached, similar differences in the pharmacokinetic parameters were observed between the two groups (Fig. 1 and Table 2). Although the mean C_{max} was practically identical (patients 112 ng · ml^{-1}, healthy subjects 116 ng · ml^{-1}), the AUC_τ was approximately 23% higher in the patients in comparison with the healthy subjects (1080 ng · h · ml^{-1} vs 880 ng . h · ml^{-1}). In addition, the elimination half-life was prolonged in the patients by 20% (12 h vs 10 h).

A comparison of the pharmacokinetic parameters in healthy subjects on days 1 and 7 revealed only a minor influence of multiple dosing. The mean C_{max} was approximately 22% higher on day 7 (116 ng · ml^{-1} vs 95.2 ng · ml^{-1}) and the mean elimination half-life increased slightly from 9.3 h on day 1 to 10 h on day 7. The $AUC_{0-\infty}$ on day 1 (909 ng.h · ml^{-1}) was almost identical to the AUC_τ on day 7 (880 ng.h · ml^{-1}), and therefore a R_x value of 1.0 (±0.38) was obtained. A moderate accumulation was observed following multiple dosing on day 7. The accumulation calculated by "AUC_τ (*day 7*)/AUC_τ (*day* 1)" amounted to 1.24.

The pharmacokinetics of candesartan in the patients with liver disease on day 1 were similar to those on day 7: the mean C_{max} on day 1 (109 ng · ml^{-1}) was practically the same as on day 7 (112 ng · ml^{-1}), the mean elimination half-life remained unchanged (12 h on day 1 and day 7) and the AUC ratio R_x = AUC_τ (day 7)/$AUC_{0-\infty}$ (*day 1*) was 1.0 (±0.31). The accumulation factor R was 1.21 and this corresponds well with the accumulation in the healthy volunteers.

The C_{min} in healthy volunteers on days 2, 5, 6 and 7 varied between 10.2 ng · ml^{-1} and 12.3 ng · ml^{-1} and reflect low inter-day fluctuation. The corresponding values in the patients with liver disease also showed a low fluctuation ranging from 13.7–15.5 ng · ml^{-1}.

An unpaired *t*-test procedure was used to compare the kinetic parameters of healthy volunteers and patients with liver impairment. At a confidence level of 95% (α = 0.05), no difference was found between the two groups regarding the kinetic parameters obtained on day 1 or day 7.

Serum protein binding

The free fraction (f_u) of candesartan in serum was approximately 0.5%. There were no significant differences between patients with liver disease and healthy subjects and between days 1 and 7. In three patients, the free fraction was 0.6–0.7%.

Adverse events

Candesartan cilexetil was well tolerated in the patients and the healthy subjects. A total of seven adverse events (diarrhoea, bronchitis and tiredness) were reported by two patients, while four adverse events (paresthesia and tiredness) were experienced by three healthy volunteers. No subjects were withdrawn due to adverse events. There were no clinically significantly changes in clinical laboratory measurements, in heart rate, blood pressure, ECG or prothrombin time (Table 1).

Discussion

The present study was designed to compare single- and multiple-dose pharmacokinetics of candesartan in patients with mild to moderate liver disease and healthy volunteers. Up to 30% of an oral dose is metabolized in the liver to inactive metabolites [5], and any impairment of this metabolic degradation might result in unusually high drug concentrations, leading to unwanted pharmacological and adverse effects.

The pharmacokinetics of candesartan in healthy volunteers following single or multiple oral dosing of 12 mg candesartan cilexetil were in good agreement with previously reported data (single dose [3, 5, 9], multiple dose [10]). The inter-subject and intra-subject variation of the kinetic data of this study was low.

Only minor, statistically insignificant pharmacokinetics differences were observed between the patients with liver diseased and the healthy subjects following single dose administration and after multiple dosing. On day 1, the mean C_{max} in the patients was increased by 14%, the elimination half-life was prolonged by 29% and the AUC was increased by 21–24% in comparison with the healthy subjects. On day 7 similar minor changes were observed. These differences will have no clinically relevant consequences and dose adjustments are not required.

The pharmacokinetics of candesartan remained linear with repeated administration and there was no evidence of induction or inhibition of the candesartan-eliminating/metabolizing enzymes.

Drug accumulation was moderate and the accumulation factor R was almost identical in the patients with liver disease and the healthy volunteers. The values for R are in excellent agreement with the theoretical accumulation factors (R = 1.2 − 1.3) which can be predicted according to $R = 1/1 - e^{\beta\tau}$ (where $\beta = 0.693/t_{½}$ and τ = dose interval) [8]. The agreement between the observed and predicted accumulation confirm the linearity and predictability of candesartan pharmacokinetics. With moderate accumulation of candesartan during once-daily dosing, dose adjustments such as the use of a loading dose or an increase in the dosing interval are not likely to be required.

The possibility cannot be excluded that more pronounced and clinically significant changes could occur in patients with more severe hepatic impairment.

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