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# Evaluation of the Effect of Candesartan Cilexetil on the Steady-state Pharmacokinetics of Tacrolimus in Renal Transplant Patients

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**ABSTRACT:** *Background*. Candesartan cilexetil is a possible treatment for hypertension in renal allograft recipients. Tacrolimus is widely used as an immunosuppressant following renal transplantation. The aim of this study was to evaluate the effect of multiple doses of candesartan cilexetil on the steady-state pharmacokinetics of tacrolimus.

*Methods*. Twelve patients received oral doses of tacrolimus twice daily for 12 days from study day −2 until day 10, single oral doses of candesartan cilexetil placebo on study days −2 to −1, single oral doses of 2 mg candesartan cilexetil once daily on study days 1 to 3, oral doses of 4 mg candesartan cilexetil once daily on study days 4 to 6, and oral doses of 16 mg candesartan cilexetil once daily on study days 7 to 9. Serial blood samples were collected on days −1, 6 and 9 and were analysed for tacrolimus using microparticle enzyme immunoassay.

*Results*. Mean $C_{max,ss}$ and $AUC_{\tau,ss}$ values for tacrolimus on day 6 (4 mg candesartan) and day 9 (16 mg candesartan cilexetil) were similar to those on day −1 (tacrolimus alone). Renal function did not change under treatment with candesartan cilexetil compared with baseline. The co-administration of multiple oral doses of cardesartan cilexetil with oral doses of tacrolimus was well tolerated.

*Conclusions*. Concomitant administration of multiple doses of candesartan cilexetil does not alter the steady-state pharmacokinetics of tacrolimus. 

**Key words:** candesartan cilexetil; tacrolimus; drug interaction

## Introduction

In recent years, blockade of the renin-angiotensin system has proved beneficial in diseases such as hypertension, ischaemic heart disease and diabetic nephropathy. Following transplantation, the occurrence of chronic allograft nephropathy in renal allograft recipients often leads to deterioration of graft function and eventual graft loss. In addition to the control of hypertension and the reduction of other cardiovascular-related diseases, blockade of the renin-angiotensin system may prove helpful in prolonging graft half-life. Many drugs useful in the treatment of patients after kidney transplantation have the potential to interact with the metabolism of the commonly used immunosuppressive drugs—cyclosporine and tacrolimus. Before angiotensin receptor blockers can be established as effective substances in the treatment of patients following kidney transplantation, their interaction with immunosuppressive drugs had to be excluded.

Candesartan cilexetil is a long-acting selective angiotensin II type 1 ($AT_1$) receptor blocker. It is

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administered orally as candesartan cilexetil, which is completely converted during enteric absorption to the active compound candesartan. Candesartan cilexetil is rapidly absorbed after oral administration with peak plasma concentrations achieved after approximately 4 h. Plasma protein binding is high (>99%). It is mainly excreted unchanged through renal and biliary routes. The plasma elimination half-life is approximately 9 h [1,2].

Tacrolimus, an effective immunosuppressive compound, is similar to cyclosporine and acts by inhibiting calcineurin phosphatase. It is widely used after organ transplantation for the prevention of acute (and chronic) rejection. Its absorption from the gastrointestinal tract is variable and results in an absolute bioavailability of approximately 20%. Tacrolimus has a high affinity to red blood cells with a partition between blood and plasma of 20:1. In plasma 98.8% of tacrolimus is bound to protein. Tacrolimus is metabolized extensively with an elimination half-life of 12–15 h; 1% of the drug is excreted unchanged in urine [3].

As tacrolimus has a relatively small therapeutic margin, an interaction of the drug with candesartan cilexetil is possible and is therefore of special interest with regard to renal transplantation.

The aim of this study was to investigate the effect of co-administration of multiple doses of once daily candesartan cilexetil on the steady-state pharmacokinetics of tacrolimus in renal allograft recipients.

## Patients and Methods

### *Ethics and legal aspects*

The study was conducted in accordance with the revised Declaration of Helsinki [4], in compliance with the German Medicines Act (AMG) [5] and in sound relation with the Note for Guidance on Good Clinical Practice (GCP) [6] at the Universitätsklinikum Essen in Essen, Germany.

All study participants were given verbal and written information about the drugs, the study procedures and their rights. All participants gave their written informed consent before taking part in the study. The study was approved by the Ethics Committee of the Medizinische Fakultät Essen.

### *Patients*

Twelve male and female hypertensive patients with stable, moderate impairment of renal function after renal transplantation completed the study. Inclusion criteria were as follows: patients had to be at least 1 year post-transplantation, with a reasonably good transplant function determined by a serum creatinine value of $\leqslant 2.5$ mg/dl. Patients with any severe cardiac or pulmonary disease, or other clinically relevant findings in health status were to be excluded from participating in the study.

A significant renal transplant artery stenosis was excluded by Duplex-ultrasound. The immunosuppressive regimen was tacrolimus-based and permitted the immunosuppressive concomitant medications prednisone and mycophenolate mofetil. All patients were pretreated with angiotensin converting enzyme (ACE)-inhibitors or $AT_1$-receptor blockers. Concomitant antihypertensive therapy, such as ACE-inhibitors, angiotensin $AT_1$-receptor antagonists (other than candesartan) and histamine $H_2$-blockers were not permitted as co-medication during the entire study and were to be discontinued at least 1 week before the first administration of study medication. This period included at least 10 half-lives of the specific medication in order to exclude any pharmacokinetic interaction. Any contraindications labelled for angiotensin $AT_1$-receptor antagonists, except kidney transplantation, were not allowed.

### *Study design*

The study was carried out as an open-label, one-period, rising-dose, drug interaction study with repeated measurements on pharmacokinetic and safety parameters. Each patient was treated with oral doses of tacrolimus according to his individual dose adjustment (twice daily as close as possible to 8:00 a.m. and 8:00 p.m., the individual dosing scheme was maintained for each patient during the study) during the 12 study days (study days −2 to 10). Candesartan cilexetil was

co-administered as follows during four consecutive treatment periods of the study:

- On study days −2 to −1: Oral doses of candesartan cilexetil placebo once daily.
- On study days 1 to 3: Oral doses of 2 mg candesartan cilexetil once daily.
- On study days 4 to 6: Oral doses of 4 mg candesartan cilexetil once daily.
- On study days 7 to 9: Oral doses of 16 mg candesartan cilexetil once daily.

The 3-day treatment days for each candesartan dose-level were sufficient to achieve steady state pharmacokinetics.

Candesartan cilexetil was administered as close as possible to 08:00 a.m. in the morning. The morning dose of tacrolimus was administered concomitantly with candesartan cilexetil. There was no washout period between the different doses of candesartan cilexetil.

During this study meals were standardized and identical for all patients with respect to composition and amount, and served at predefined times.

The pharmacokinetic characteristics of tacrolimus in blood were determined on day −1 (prior to candesartan dosing), and on days 6 and 9 (with multiple candesartan cilexetil dose levels at steady-state tacrolimus pharmacokinetics).

On study day −1, a blood sample was taken predose of candesartan cilexetil and on study day 9 for determination of candesartan plasma concentrations.

### *Safety evaluation*

Kidney function, according to creatinine clearance ($2 \times 2$ h) was determined at screening and in the morning on study days −1, 6 (co-administration with 4 mg candesartan cilexetil) and day 9 (co-administration with 16 mg candesartan cilexetil). The validity and reproducibility of this method ($2 \times 2$ h rather than 24 h) had been demonstrated in a previous study comparing both creatinine clearance measurements using both methods [7].

Adverse events were ascertained on each study day, laboratory examinations (haematology, clinical chemistry and urinalysis) and a 12-channel ECG were carried out in the morning at screening (day −1) and at final check on day 10. Systolic and diastolic blood pressure, as well as pulse rate, were measured in the morning at screening (day −1) and at final check on day 10 after 15 min in a sitting position, and on study days 3, 6 and 9 at predose and 4 h a.a. A physical examination was performed at screening on day −1 and at the end of the study on day 10.

### *Analytical method*

Blood samples (2.7 ml) for the determination of tacrolimus blood concentrations were taken in EDTA containing tubes (Monovette® Sarstedt) on study days −1, 6 and 9 at 0, 1, 2, 3, 4, 6, 8, 9 and 10 h after the morning administration. Until laboratory analysis up to 4 days after blood sampling, the samples were stored at room temperature (tacrolimus is stable for up to 7 days at room temperature).

Bioanalysis of tacrolimus was carried out by the nephrology laboratory of the Universitätsklinikum Essen, using a microparticle enzyme immunoassay. The limit of quantification for tacrolimus in blood of this method was 1 g/l.

### *Pharmacokinetic methods*

Steady-state pharmacokinetic parameters for tacrolimus given twice daily on days −1, 6 and 9 were calculated for each patient using non-compartmental analysis of blood concentration-time data. Maximum blood concentrations ($C_{max,ss}$) were recorded as observed. Values for area under the blood concentration-time profile ($AUC_{\tau,ss}$) were estimated using the linear trapezoidal rule, and were calculated from time zero to 12 h (extrapolated from time 10 h to 12 h) after administration on days −1, 6 and 9. Additionally, the secondary pharmacokinetic parameters $C_{av}$, $C_{min,ss}$ and peak trough fluctuation (PTF) were calculated.

### *Statistical methods*

The primary objective of this study was to investigate the effect of co-administration of multiple doses of candesartan cilexetil once daily on the steady-state pharmacokinetics of tacrolimus given twice daily.

A lack of interaction could be concluded if the rate and extent of absorption between the two test treatments (tacrolimus with different candesartan doses) and the reference (tacrolimus without candesartan) was equivalent. The equivalence was calculated by ratio analysis using the primary pharmacokinetic parameters $AUC_{\tau,ss}$ and $C_{max,ss}$, for which point estimates and 90% confidence intervals were calculated for the 100 * Test/Reference ratio (as relative bioavailability), using a multiplicative model (logarithmic transformation). The absence of a drug–drug interaction was to be concluded if for the primary characteristics, $AUC_{\tau,ss}$ and $C_{max,ss}$, the calculated 90% confidence interval for the ratios 100 * Test/Reference was within the internationally approved bioequivalence range of 80% to 125% for $AUC_{\tau,ss}$ and 70% to 143% for $C_{max,ss}$ [8].

All safety parameters were described by the following statistics: arithmetic means, standard deviations, medians, minimum and maximum values, coefficient of variation. All adverse events were listed. Treatment-emergent adverse events were summarized.

## Results

### *Study population*

Twelve patients were enrolled into the study. There were two drop-outs, one due to dizziness; the other due to the intake of forbidden concomitant medication. Both drop-outs were replaced. Twelve patients (5 male, 7 female) completed the study. The mean age of these patients was 51.8 years (range 27–63 years) and their mean weight was 76.2 kg (range 60–92 kg) (Table 1).

### *Pharmacokinetics*

The blood tacrolimus concentration-time profiles after co-administration of tacrolimus with 4 mg (day 6) and 16 mg (day 9) candesartan cilexetil both superposed upon that of tacrolimus alone (day −1) (Figure 1).

Individual differences in the pharmacokinetic parameters of tacrolimus are summarized in Table 2. There was a negligible difference in the mean $AUC_{\tau,ss}$ and mean $C_{max,ss}$ values between the three treatments, indicating minimal changes in steady-state tacrolimus pharmacokinetics after co-administration with candesartan cilexetil compared with administration of tacrolimus alone. There was no statistically significant difference between the extent and rate of tacrolimus metabolism under co-administration of multiple doses of candesartan cilexetil compared with the tacrolimus administration without candesartan cilexetil, indicating no effect of candesartan cilexetil on the steady-state pharmacokinetics of tacrolimus (Table 3).

Table 1. Demographic data. Descriptive statistics. Per protocol population

| Sex (male/female) | 5/7 | |
|---|---|---|
| | Mean (± SD when indicated) | Range |
| Age (years) | 51.8 ± 10.45 | 27–63 |
| Body weight (kg) | 76.2 ± 11.16 | 60–92 |
| Time since transplantation (years) | 6.17 ± 3.79 | 3–15 |
| Serum creatinine (mg/dl) | 1.41 ± 0.459 | 0.8–2.4 |
| Mean tacrolimus dose (mg/day) | 3.96 ± 2.12 | 2–9 |

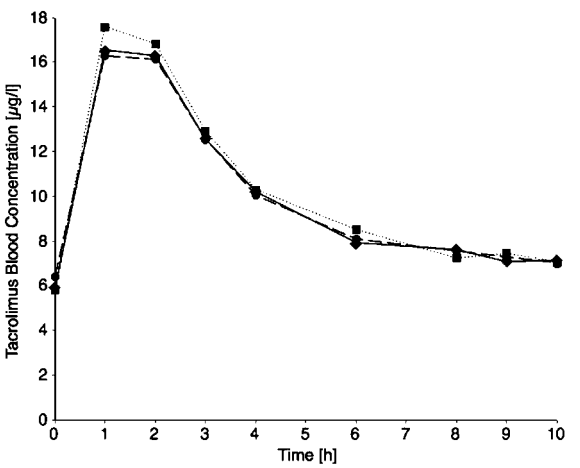


Figure 1. Pharmacokinetic profiles of tacrolimus blood concentrations in the steady state taken b.i.d. either without candesartan cilexetil on day −1 (solid line, diamonds), with 4 mg candesartan cilexetil o.a.d. on day 6 (dashed line, circles), or with 16 mg candesartan cilexetil o.a.d. on day 9 (dotted line, squares), respectively (each point represents the geometric mean of $n = 12$ patients)

Table 2. Geometric mean (geometric standard deviation) ($n = 12$) of the model independent primary and secondary target parameters of tacrolimus in whole blood following repeated dose administrations on study days −1, 6 and 9

| Pharmacokinetic characteristics [Unit] | Tacrolimus alone | Tacrolimus together with 4 mg Candesartan Cilexetil | Tacrolimus together with 16 mg Candesartan Cilexetil |
|---|---|---|---|
| | day −1 | day 6 | day 9 |
| Primary target parameter | | | |
| $AUC_{\infty,ss}$ [g*h/l] | 115.61 (1.25) | 115.46 (1.27) | 118.25 (1.29) |
| $C_{max,ss}$ [g/l] | 18.23 (1.37) | 17.42 (1.33) | 19.03 (1.47) |
| Secondary target parameter | | | |
| $C_{av}$ [g/l] | 9.63 (1.25) | 9.62 (1.27) | 9.85 (1.29) |
| $C_{min,ss}$ [g/l] | 5.69 (1.23) | 6.20 (1.29) | 5.80 (1.20) |
| PTF [%] | 126.84 (1.32) | 112.44 (1.41) | 130.84 (1.38) |

Table 3. Point estimates (relative bioavailability), 90% confidence intervals, and ANOVA CVs for $AUC_{\tau,ss}$ and $C_{max,ss}$ of tacrolimus in whole blood for comparisons of the test treatments (co-administration of candesartan cilexetil) with the reference tacrolimus alone

| | | Tacrolimus $AUC_{\tau,ss}$ | Tacrolimus $C_{max,ss}$ |
|---|---|---|---|
| Intraindividual ratio 4 mg Cardesartan*100/placebo | Geometric mean [%] | 99.87 | 95.55 |
| | 90% Confidence interval [%] | 87.72–113.71 | 81.14–112.53 |
| | ANOVA CV [%] | 15.91 | 20.13 |
| Intraindividual ratio 16 mg Candesartan*100/placebo | Geometric mean [%] | 102.28 | 104.39 |
| | 90% Confidence interval [%] | 81.14–112.53 | 88.64–122.94 |
| | ANOVA CV [%] | 15.91 | 20.13 |

## *Safety parameters*

*Creatinine clearance and blood pressure*. Descriptive statistics of creatinine clearance did not reveal any relevant changes over the trial (Table 4). Systolic and diastolic blood pressure remained stable during the trial (Table 5).

Table 4. Descriptive statistics of creatinine clearance [ml/min] on days −1, 6 and 9 (mean, SD). Safety population (days −1, 6: $n = 14$, day 9: $n = 12$), pooled data from the 0–2 h and 2–4 h interval

| Time interval | Creatinine clearance (ml/min) |
|---|---|
| | 0–4 h |
| Day −1 | 62.8 ± 19.5 |
| Day 6 | 64.4 ± 22.0 |
| Day 9 | 60.7 ± 22.7 |

*Adverse events*. During the study, nine treatment-emergent adverse events occurred (Table 6). Five of them were assessed as unlikely/not related, and four as possibly or probably study drug-related. The adverse events assessed as not study drug-related were headache in three cases, and once nausea and toothache. The adverse events assessed as study drug related were dizziness, headache, diarrhoea and worsening of arthralgia (all in one patient). The symptom dizziness was first assessed as mild, but then worsened and was assessed as severe on day 6. At the same time a clear decrease in systolic blood pressure was evident. Consequently, the study drug dosage was reduced from 16 mg candesartan to

Table 5. Descriptive statistics of blood pressure during screening and final check (mean, SD). Safety population (day −1: $n = 12$, day 10: $n = 14$)

| Study day | Blood pressure (mmHg) | |
|---|---|---|
| | Systolic | Diastolic |
| Day −1 | 138.5 ± 11.4 | 84.2 ± 8.6 |
| Day 10 | 136.2 ± 19.1 | 84.9 ± 7.7 |

Table 6. Frequency of treatment emergent AEs, broken down by relation to study medication, occurring over the study

| Adverse event | Not related | Related |
|---|---|---|
| Dizziness | 0 | 1 |
| Headache | 3 | 1 |
| Diarrhoea | 0 | 1 |
| Nausea | 1 | 0 |
| Toothache | 1 | 0 |
| Arthralgia | 0 | 1 |

4 mg candesartan on days 7 and 8. The subject received the last dosage of candesartan on day 8. After discontinuation of the study medication the symptoms resolved without any sequelae.

There were no safety-relevant findings in laboratory values, vital signs and physical examination. Mean and median of creatinine clearance did not reveal any relevant changes over the trial.

## Discussion

The clinical utility of tacrolimus as an immunosuppressive drug is complicated by its narrow therapeutic margin, as well as its inter-and intra-individual variable pharmacokinetics. An increase in tacrolimus exposure increases the risk of adverse effects, such as changes in glucose metabolism, neuro- and nephrotoxicity and over-immunosuppression; whereas a reduction increases the risk of allograft rejection. As a substrate of cytochrome P450 (CYP) 3A4 enzymes and P-glycoprotein, tacrolimus interacts with several drugs which are known CYP3A4 and P-glycoprotein inhibitors or inducers [9]. The cytochrome involved in candesartan metabolism has been identified as CYP2C9. Candesartan is metabolized only to a small extent and is excreted unchanged. So far, there has been no evidence for the inhibition or induction of CYP3A4 and CYP2C9 by candesartan cilexetil [10]. The results of this study indicate that candesartan does not interfere with the rate or extent of tacrolimus absorption, based on the fact that the mean $AUC_{\tau,ss}$ and $C_{max,ss}$ values for tacrolimus obtained after co-administration with different doses of candesartan were comparable to corresponding values obtained after administration of tacrolimus alone. An inhibition or induction of CYP3A4 and P-glycoprotein by candesartan cilexetil is therefore unlikely. Thus, it could be concluded that the concomitant administration of multiple doses of candesartan does not alter the steady-state pharmacokinetics of tacrolimus.

Overall, treatment with candesartan cilexetil and tacrolimus was safe and well tolerated with respect to the number of adverse events, as well as the course of blood pressure and creatinine clearance over the trial.

In view of the results of this study, it is feasible that the indication for candesartan cilexetil can be broadened to include renal transplant patients. However, the extent to which candesartan cilexetil prevents graft loss in renal allograft recipients remains to be evaluated in further studies.

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