ELSEVIER

INTERACTIONS OF SILDENAFIL AND TACROLIMUS IN MEN WITH ERECTILE DYSFUNCTION AFTER KIDNEY TRANSPLANTATION

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ABSTRACT

Objectives. To study the pharmacokinetics of the combined use of sildenafil (which may provide an effective treatment for patients with erectile dysfunction after kidney transplantation) and tacrolimus, as interactions between them are expected because of a common elimination pathway.

Methods. Ten male patients (age 29 to 52 years) were included. Because of its importance in transplant recipients, medication remained unchanged. On day 1, tacrolimus was administered routinely, and blood samples for tacrolimus assays were drawn at predefined times. On day 2, sildenafil was added and blood was collected for assays of tacrolimus, sildenafil, and the sildenafil metabolite UK103,320 (UK) at the indicated times. Blood pressure was monitored on both study days. Sildenafil and UK were assessed by high-pressure liquid chromatography and tacrolimus was assessed by microparticle enzyme immunoassay.

Results. No effects of sildenafil on the tacrolimus pharmacokinetics were found. However, in the patients studied, the sildenafil and UK pharmacokinetics were altered compared with the results of previous studies. The mean peak concentration of sildenafil was higher by 44% and the area under the concentration-time data increased by 90%. The elimination half-life was prolonged (4.7 hours compared with 3 hours in healthy volunteers). The area under the concentration-time data for UK was about threefold larger than in healthy volunteers, and the half-life was prolonged from 3.8 hours to 11.4 hours. Pronounced blood pressure drops were observed.

Conclusions. Tacrolimus or the concomitant medication or the disease itself might have altered the sildenafil and UK pharmacokinetics. Because of the drop in blood pressure, sildenafil therapy should start at the lowest dose and any antihypertensive medication should be adjusted. UROLOGY **58:** 589–593, 2001.

After kidney transplantation, 50% to 60% of male patients have erectile dysfunction (ED).[1] Our patients described ED as more severe than during hemodialysis therapy. To date, no explanation is sufficient for this aggravation. Immunosuppressive or concomitant medication might be responsible. Without treatment, ED may severely impair the patient's and his partner's quality of life. Failure and partnership conflicts and feelings of guilt and depression are frequently reported. Therefore, sildenafil (Viagra) may become an important treatment option for these patients. A pharmacokinetic interaction between sildenafil and tacrolimus might exist, because both drugs share a common metabolism pathway by way of the cytochrome P4503A4 enzyme system (CYP3A4). Because no data have yet been published concerning the combined application of both substances, the aim of this study was to analyze the pharmacokinetic characteristics of tacrolimus and sildenafil with concomitant application. After transplantation, tacrolimus and other concomitant drugs cannot be omitted from immunosuppressive treatment, which did not allow us to use the optimal design for an interaction study. Therefore, the pharmacokinetic characteristics for sildenafil as provided by the manufacturer served as the control.

After oral application to healthy volunteers, the

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absorption of tacrolimus is variable and incomplete, with a bioavailability of ~25%. It is influenced by the intake of food with a high fat or carbohydrate content. The peak concentrations in whole blood are observed ~2 hours after oral administration and vary widely. The protein binding of tacrolimus is ~99%. Because of its strong affinity to erythrocytes, the whole blood concentrations are about 15 to 35-fold higher than those measured in plasma. Tacrolimus is primarily metabolized in the liver by hydroxylation and demethylation by way of CYP3A4 into at least 9, possibly 15 or more, different metabolites, 1 of which has an efficacy comparable to tacrolimus itself. Elimination of the metabolites takes place mainly by way of the biliary system.[2]

Sildenafil is rapidly absorbed after oral administration, and peak plasma levels occur within 1 hour. The absolute bioavailability is 41%. Plasma protein binding is 96%. Like tacrolimus, sildenafil is primarily metabolized by CYP3A4. The active metabolite (UK103,320) is formed through *N*-demethylation and is metabolized further. Its potency is about 50% of the parent compound.[3]

MATERIAL AND METHODS

Patients

Ten male patients with ED, who were 29 to 52 years old (mean 42.5), were included in the study. The diagnosis of ED was based on the medical history, physical examination, penile duplex ultrasonography, intracavernosal injection of 10 or 20 μg alprostadil, and endocrinologic tests. The mean interval after kidney transplantation was 43.3 months (range 22 to 67). All patients received immunosuppressive therapy that included tacrolimus. After approval of the local ethics committee, patients were provided detailed information about the proceedings, risks, and possible adverse effects and gave informed consent. The exclusion criteria were contraindications for sildenafil, creatinine clearance less than 30 mL/min, penile deformities, concomitant treatment for ED, medication with cumarin derivatives, severe coagulopathy, active peptic ulcers, and diseases predisposing toward priapism.

The causes for terminal kidney failure were chronic glomerulonephritis (8 cases), Alport syndrome (1 case), and diabetic nephropathy (1 case). Prior and concomitant diseases were arterial hypertension (10 cases), renal anemia (6 cases), hyperlipoproteinemia (3 cases), diabetes mellitus (2 cases), secondary hyperparathyroidism (1 case), and chronic bronchitis (1 case). The waiting period before transplantation was 35.5 months (range 6 to 77).

Two patients had had ED since puberty, and in 6 patients, ED occurred with the increasing severity of renal disease and dialysis. Four of these patients complained of severe deterioration after transplantation and 2 patients experienced ED for the first time after transplantation. The origin of ED was arterial-vascular dysfunction in 5 cases; additional reasons were veno-occlusive dysfunction and psychological factors. No obvious reason could be found in 3 patients; possibly the immunosuppressive or concomitant medication caused the ED.

The mean creatinine level during observation was 2.0 mg/dL (range 1.4 to 2.9); the creatinine clearance was 55.3 mL/min (range 33 to 85). Tacrolimus was administered twice daily with an individual dose between 0.5 and 3 mg. Concomitant medication contained azathioprine or mycophenolate mofetil, verapamil, and acetylsalicylic acid. Additionally, prednisolone, angiotensin-converting enzyme inhibitors, angiotensin I receptor antagonists, vitamin D, ferric preparations, iodine preparations, erythropoietin, ranitidine, 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors, omeprazole, allopurinol, theophylline, polysulfone acid, biguanides, and insulin were used individually. None of these individual dosing regimes were changed during the study.

Study Procedure

The tacrolimus concentrations were assessed in whole blood. As a reference, blood samples without sildenafil, but with the concomitant medication as described above, were taken before and 1, 2, 4, 8, and 12 hours after administration. On day 2, tacrolimus and 50 mg sildenafil were administered simultaneously, along with the concomitant medication. The samples for determination of tacrolimus, sildenafil, and UK103,320 concentrations were taken before and 0.5, 1, 1.5, 4, 8, 12, and 24 hours after administration. Blood pressure was monitored on both trial days before and 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours after intake to examine the effects of sildenafil on the patients' blood pressure.

Analytics

Immediately after collection, heparinized sample tubes for the assay of sildenafil and UK103,320 concentrations were centrifuged at 1500*g* for 10 minutes and stored at −20°C. Sildenafil and UK103,320 were assessed by high-pressure liquid chromatography. First, both substances were extracted from plasma with tert-butyl-methyl-ether. Dried extracts were reconstituted in 150 μL of eluent, and 50 μL were injected into a high-pressure liquid chromatography/MS system (Shimadzu QP8000, Kyoto, Japan). The peaks of the mass 475.4 amu (sildenafil H+) and the mass 440.2 amu (metabolite H+) were recorded. The peak heights of the drugs were used to construct the calibration curves. The procedure has been shown to be selective for sildenafil and UK103,320 and is linear over the range 2.0 to 500.0 ng/mL. The within-batch variability (n = 6) for the sildenafil concentrations ranged from 3.6% to 8.8% at 5.2 ng/mL, 0.9% to 5.9% at 51.6 ng/mL, and 1.3% to 3.6% at 258.2 ng/mL. The batch-to-batch variability ranged between 2.6% and 7.8% (n = 18). The precision determined as the percentage of nominal concentration ranged between 92.7% and 104.6% for sildenafil. The within-batch variability (n = 6) for the UK103,320 concentrations ranged from 4.0% to 15.3% at 5.2 ng/mL, 2.5% to 9.4% at 51.4 ng/mL, and 10.3% to 17.0% at 257.0 ng/mL. The batch-to-batch variability ranged between 12.7% and 16.7% (n = 18). The precision determined as the percentage of nominal concentration ranged between 82.0% and 107.3% for UK103,320. The correlation coefficient of the three different batches was greater than 0.9984 for sildenafil and greater than 0.9828 for the metabolite (n = 8 for the different calibration concentrations).

The concentrations of tacrolimus in whole blood were measured according to routine procedures on the day of collection using a microparticle enzyme immunoassay (MEIA, Tacrolimus 2, Abbott Laboratories, Abbott Park, Ill).

Statistical Analysis

The concentration-time profile and pharmacokinetic characteristics were obtained by model-independent evaluation methods using the HOEREP-PC program[4]. In the case of tacrolimus, the maximal concentration and the area under the concentration-time data for one dosing interval (AUC) were normalized for a dose of 1 mg twice daily. The time to reach the maximal concentration, relative total clearance, terminal

TABLE I. ***Concentration-time profile and pharmacokinetic characteristics for tacrolius, sildenafil, and its metabolite UK103,320 (n = 10)***

	Tacrolimus		Sildenafil			
			Results of This Study		Historical Data	
	Without Sildenafil	With Sildenafil	Sildenafil	UK103,320	Sildenafil	UK103,320
c_{max} (ng/mL)*	15.6 ± 7.40	14.8 ± 7.69	390 ± 149	118 ± 42.1	271†	126†
t_{max} (hr)	1.80 ± 1.23	1.45 ± 0.96	0.75 ± 0.49	1.80 ± 1.32	0.79†	0.78†
AUC [ng · hr/mL]*	119 ± 62.1	124 ± 62.9	1405 ± 578	932 ± 447	738†	328†
CL/f (L/hr)	10.4 ± 4.91	10.0 ± 4.74	39.9 ± 12.7	63.6 ± 24.7	58‡	NA
MT (hr)	17.6 ± 3.08	21.3 ± 6.46	5.90 ± 1.37	11.4 ± 2.64	NA	NA
$t_{50\%}$ (hr)	11.8 ± 2.75	14.5 ± 4.52	4.70 ± 1.39	8.62 ± 2.67	3.0†	3.5†

*KEY: c_{max} = maximal concentration; t_{max} = time to reach maximal concentration; AUC = area under the concentration-time data (see * footnote); CL/f = relative total clearance; MT = total mean time; $t_{50\%}$ = terminal half-life.*

** For tacrolimus, AUC represents the area under the concentration-time data for one dosing interval; furthermore, the maximal concentration (c_{max}) and the area under the concentration-time data for one dosing (AUC) were normalized for a dose of 1 mg twice daily. For sildenafil and UK103,320, AUC represents the area under the concentration-time data completed by extrapolation.*

† Unpublished results (Pfizer GmbH, Karlsruhe, Germany).

‡ Summary of product characteristics (Pfizer GmbH, Karlsruhe, Germany).

half-life, and total mean time are reported as determined. For sildenafil and UK103,320, the same characteristics were determined without normalization for dose, because all patients received the same dose of 50 mg. For sildenafil and UK103,320, the AUC represents the area under the data completed by extrapolation. The evaluation for a possible drug-drug interaction followed the method proposed by Steinijans *et al.*[5] The previously mentioned variables were subjected to an analysis of variance with treatment and subject as the main effects based on ln-transformed data (except for the time to reach the maximal concentration). The mean square error was used to construct 90% conventional confidence intervals. For the time to reach the maximal concentration, a nonparametric approach was used.[6]

RESULTS

PHARMACOKINETICS

The concomitant administration of a single dose of 50 mg sildenafil did not exert any effect on the tacrolimus pharmacokinetics (Table I). As a measurement for a possible drug-drug interaction, the following point estimates (ratio test over reference) and 90% confidence intervals for log-transformed data were evaluated: maximal concentration, 93% (73% to 118%); AUC(0-τ), 104% (91% to 119%); relative total clearance, 96% (84% to 110%); total mean time, 117% (97% to 142%); and terminal half-life, 119% (100% to 141%). In particular, the AUC and relative total clearance indicate that an interaction between tacrolimus and sildenafil is unlikely. The wider confidence interval for the remaining characteristics was primarily due to the relatively small number of patients enrolled in the study.

The pharmacokinetic characteristics of sildenafil and UK103,320 for kidney transplant patients studied in this trial differed from those of healthy volunteers provided by the manufacturer (Table I).

The maximal plasma concentration of sildenafil was higher (44%), and, because of the reduced relative total clearance, the AUC was 90% larger. The elimination half-time was prolonged (ie, 4.7 hours compared with 3 hours in healthy volunteers). The total mean time of sildenafil was 5.9 hours.

The peak concentrations of the main metabolite correspond to the manufacturer's data. The relative total clearance of UK103,320 was 63.6 L/hr. The AUC was 2.8-fold larger than in healthy volunteers, and the elimination half-time was 8.6 hours, considerably longer than in healthy persons (3.5 hours). The total mean time was 11.4 hours. It has been previously reported that the AUC of the metabolite is about 40% of the AUC of the parent drug[3]; the metabolite exerts about 50% of its efficacy. In this study, the AUC of UK103,320 showed 66% of the AUC of sildenafil. Therefore, a higher efficacy in transplanted patients might result.

According to the pharmacokinetic characteristics determined in this study and used in a computer simulation with daily intake of a single, 50-mg dose, a clinically relevant accumulation of sildenafil or UK103,320 is not expected.

ADVERSE EFFECTS

Five patients reported mild adverse effects, including headache (2 cases), drowsiness (1 case), gastric disorders (1 case), and nasal congestion (1 case).

However, after sildenafil administration, pronounced decreases in blood pressure, compared with the values with the unchanged concomitant medication, were observed. The maximal differences in systolic and diastolic blood pressure were a mean of 27 mm Hg (range 5 to 50) and 20 mm Hg (range 11 to 35), respectively. The point of maximal decrease in the systolic and diastolic blood pressure varied among the patients. The maximal difference in the mean arterial blood pressure (MAP) was 20 mm Hg (range 13 to 37). Figure 1 shows the mean MAP on the trial days with and

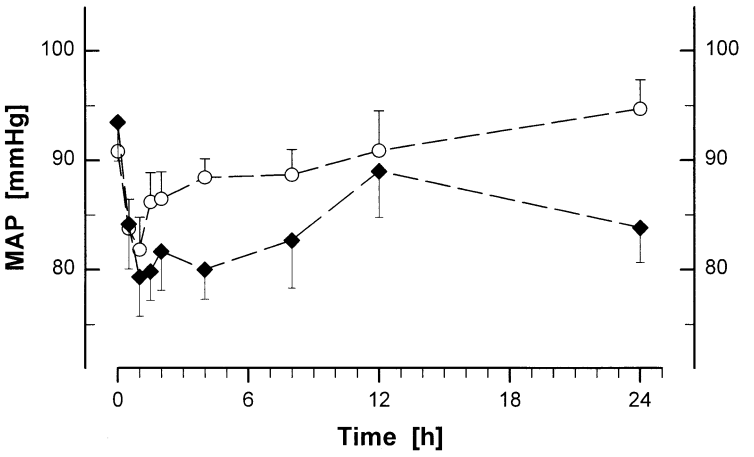

FIGURE 1. *MAP after intake of routine medication (circles) and after additional application of 50 mg sildenafil (diamonds). A dose of 50 mg sildenafil led to a remarkable decrease in blood pressure, which remained throughout the 24-hour observation period (mean values, standard error of the mean, n = 10).*

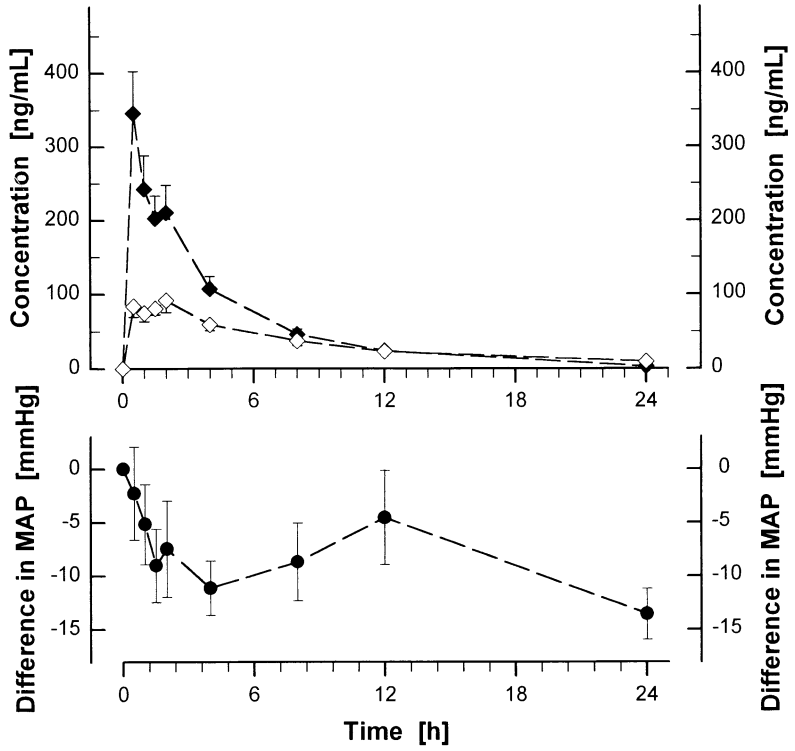

FIGURE 2. *Plasma levels of sildenafil (black diamonds) and UK103,320 (white diamonds) and an additional drop of the MAP after application of 50 mg sildenafil (circles) (mean values, standard error of the mean, n = 10).*

without sildenafil. Although the MAP returned to the baseline values after 24 hours on the trial day without sildenafil, a remarkable decrease was observed even 24 hours after intake of sildenafil and was not due to the sildenafil or UK103,320 plasma concentrations, as shown in Figure 2.

COMMENT

The aim of this study was to examine the pharmacokinetic characteristics of sildenafil and tacrolimus with concomitant administration, thereby clarifying the safety of sildenafil in patients receiving immunosuppressive therapy. In this study, patients took sildenafil in addition to their daily medication, which, among others, consisted of verapamil and an angiotensin-converting enzyme inhibitor or angiotensin I receptor blocker for treatment of hypertension and nephroprotection. A single dose of 50 mg sildenafil did not affect the pharmacokinetic characteristics of tacrolimus. However, the changes in the pharmacokinetic characteristics of sildenafil and its main metabolite UK103,320 might be due to an interaction with tacrolimus, the concomitant medication, and/or the patient's disease. The substrate specificity of the CYP3A4 enzymes is very broad.[7] A large part of the concomitant medication is metabolized by CYP3A4 and might therefore alter the pharmacokinetics of sildenafil and vice versa. In this study, these included verapamil, nifedipine, omeprazole, theophylline 7, 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors, losartan,[8] and ranitidine.[9] In healthy volunteers, the AUC of the main metabolite did not ex-

ceed 30% to 40% of the sildenafil AUC.[3] The results of this study revealed a ratio of 66%. Because the main metabolite exerts about 50% of sildenafil's potency, an increased effect might result not only from the elevated sildenafil concentrations, but also from higher UK103,320 concentrations. Whether a stronger inhibition of the metabolizing enzymes occurs with daily administration, resulting in an altered elimination half-time and bioavailability, requires clarification in additional studies. A computer simulation of daily intake suggests no clinically relevant accumulation of either substance.

The observed blood pressure values were significantly lower with the addition of sildenafil. The decreased blood pressure even after 24 hours was most remarkable. At 24 hours, neither sildenafil nor its main metabolite was detectable in the plasma in relevant concentrations. It is probable that additional metabolites of sildenafil with a slow turnover caused these effects, or the metabolism of the concomitantly administered verapamil was altered, causing delayed blood pressure drops. The hypotensive effect of sildenafil has been previously described. An intake of 100 mg sildenafil by healthy volunteers led to a maximal drop of systolic and diastolic blood pressure of 10 mm Hg and 7 mm Hg, respectively.[10] In another placebo-controlled study, only the additive antihypertensive effects of sildenafil (100 mg orally) and amlodipine (5 to 10 mg/day orally) were described.[11] In the present study, the blood pressure changes were much more intense and longer lasting, despite a lower sildenafil dose.

CONCLUSIONS

We found no evidence that the pharmacokinetics of tacrolimus is affected by sildenafil. The changes in the sildenafil pharmacokinetics, with respect to on-demand use, are considered clinically manageable. Because sildenafil reached higher plasma levels and blood pressure drops were observed, a starting dose of 25 mg and, if necessary, an adjustment of any antihypertensive drugs on the days of sildenafil use is recommended. Additional investigations concerning the relevant pharmacokinetic interactions with tacrolimus in daily concomitant use with sildenafil and the efficacy of sildenafil in men after kidney transplantation are necessary. With respect to the observed blood pressure changes, interaction studies with antihypertensive drugs are of critical importance.

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