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Brief Report

Nephrology Dialysis Transplantation

Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients

Ingrid Mai, Elke Störmer, Steffen Bauer, Hagen Krüger, Klemens Budde[1] and Ivar Roots

Institute of Clinical Pharmacology and [1]Department of Internal Medicine and Nephrology, University Medical Center Charité, Humboldt University of Berlin, Berlin, Germany

Abstract

Background. This study investigated the effect of St John's wort (SJW) extract on the pharmacokinetics of the immunosuppressants tacrolimus (TAC) and mycophenolic acid (MPA).

Methods. Ten stable renal transplant patients received 600 mg SJW extract for 14 days in addition to their regular regimen of TAC and mycophenolate mofetil.

Results. Dose-corrected $AUC_{(0–12)}$ of TAC decreased significantly from 180 ng/ml/h at baseline to 75.9 ng/ml/h after 2 weeks of SJW treatment. To maintain therapeutic TAC concentrations, dose adjustments from a median 4.5 mg/day at baseline to 8.0 mg/day under SJW treatment were required. Two weeks after discontinuation of SJW, TAC doses were reduced to a median of 6.5 mg/day. MPA pharmacokinetics remained unaffected by comedication with hypericum extract.

Conclusions. Administration of SJW extract to patients receiving TAC treatment can result in a serious drug interaction leading to markedly reduced TAC blood concentrations associated with the risk of organ rejection.

Keywords: drug interaction; immunosuppression; mycophenolic acid; St John's wort; tacrolimus; transplantation

Introduction

St John's wort (*Hypericum perforatum*, SJW) extracts are increasingly used for the treatment of mild to moderate depression [1] and are available without prescription in many countries. SJW extracts contain a variety of different compounds [2], with hypericin, pseudohypericin and hyperforin presumed responsible for the drug's antidepressive activity. Chronic use of SJW has been reported to reduce the bioavailability of a number of drugs, including digoxin [3], indinavir [4] amitriptyline [5] and cyclosporine. Acute transplant rejections due to decreased cyclosporine concentrations with co-administration of SJW have been reported in several cases [6,7]. Both, metabolic (cytochrome P-450) and drug transport (P-glycoprotein) mechanisms have been discussed as the cause for the SJW drug interaction and *in vitro* studies suggest that both mechanisms contribute to the observed decrease in bioavailability under SJW [8,9].

Tacrolimus (TAC) is a macrolide immunosuppressant frequently used after kidney, liver and heart transplantations. TAC trough levels are routinely monitored and dose adjustments are made to achieve therapeutic blood concentrations of 5–15 ng/ml. Mycophenolate mofetil is a prodrug, which is rapidly absorbed and metabolized to the active compound mycophenolic acid (MPA), a reversible inosine 5′-monophosphate dehydrogenase inhibitor. Mycophenolate mofetil is typically combined with TAC or cyclosporine, because of synergistic effects from their different mechanisms of action.

The present study investigated the effects of 14 days of treatment with 600 mg hypericum extract per day on the pharmacokinetics of the immunosuppressants TAC and MPA in renal transplant patients.

Subjects and methods

Patients

Ten renal transplant patients (six male and four female) at least 2 years post-organ transplantation under stable immunosuppressant treatment with TAC (eight with mycophenolate mofetil comedication) were enrolled in the study. Patients underwent general blood and urine analysis to ensure that renal function, as assessed by creatinine levels, was stable. Patients were included if the creatinine clearance was >30 ml/min. Dietary restrictions included caffeine,

Correspondence and offprint requests to: Dr Ingrid Mai, Institut für Klinische Pharmakologie der Charité, Humboldt-Universität zu Berlin, Schumannstr. 20/21, D-10098 Berlin, Germany.
Email: ingrid.mai@charite.de

ethanol, grapefruit juice and smoking. Comediations were kept unchanged throughout the study. Detailed patient characteristics are reported in Table 1. The study was approved by the ethical committee of the Humboldt University of Berlin, and all patients consented in writing to their participation in this study. Patients were informed about an expected decrease in immunosuppressant plasma concentrations, which would be monitored in tight intervals and compensated by an increase in dose thus minimizing the risk of acute rejection.

Study design

Patients received 600 mg SJW extract (once daily two tablets Jarsin300™, Lichtwer Pharma, Berlin, Germany) for 14 days in addition to their normal regimen of TAC (Prograf™, Fujisawa Healthcare, Inc., Deerfield, IL, USA) and mycophenolate mofetil (CellCept™, Hoffmann-La Roche AG, Basel, Switzerland). TAC and MPA kinetics were measured on the day before initiation of SJW treatment and on day 14 of SJW application with sampling times of 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h post-administration of TAC and MPA. Trough levels of TAC were determined regularly throughout the study and dosage adjustments were made to keep TAC trough concentrations in the therapeutic range of 5–15 ng/ml. After the end of the study, TAC doses were adjusted to achieve typical pre-study trough concentrations for each patient. Final TAC and MPA trough levels were measured 2 weeks after discontinuation of SJW treatment. The MPA dose was 1000–2000 mg/day and as the therapeutic concentration range is yet undefined, dose changes were allowed if indicated by increased side effects. All 10 patients complied with the dosage requirements for SJW (determined by measurement of hypericin and pseudohypericin in plasma) and TAC, two patients were without mycophenolate mofetil comedication and were therefore excluded from the MPA data analysis.

Sample analysis

TAC blood concentrations were determined by microparticle enzyme immunoassay using an IM_X analyser (Abbott Laboratories, Chicago, IL, USA). MPA plasma concentrations were determined by homogenous enzyme immunoassay (Emit™ using a COBAS MIRA S analyser, Hoffmann-La Roche AG, Basel, Switzerland). Lower limits of quantification were 1.5 ng/ml and 0.1 μg/ml for TAC and MPA, respectively.

Data analysis

Compartment free pharmacokinetic analysis was conducted using WinNonLin Pro 1.5 (Pharsight Corp., Mountain View, CA, USA) to determine $AUC_{(0–12)}$, C_{max}, t_{max} and C_{trough}.

Values of AUC, C_{max} and C_{trough} for TAC were corrected for dose to account for the dosage adjustments made to achieve the required trough level.

Statistical significance between the two treatment conditions was assessed using a Wilcoxon-test (SPSS 10.0, SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant with $P < 0.05$.

Results

Tacrolimus

Co-administration of SJW extract significantly reduced the area under the plasma-concentration time curve as well as the peak and trough blood concentrations of TAC (Table 2). Median dose-corrected $AUC_{(0–12)}$ values decreased from a baseline median of 180 ng/h/ml to 75.9 ng/h/ml after 2 weeks of SJW

Table 1. Patient characteristics of enrolled renal transplant patients

No.	Sex	Age	Weight (kg)	Years post-transplant	Creatinine (mg/dl)		Urea (mg/dl)		Diagnosis	Comedication
					Baseline	SJW[a]	Baseline	SJW[a]		
1[b]	m	31	98	3	2.2	2.1	99	69	Reflux nephropathy	Furosemide, cerivastatin, methylprednisolon, benazepril
2	m	43	86	4	0.7	0.7	20	10	Chronic glomerulonephitis	Furosemide, moxonidine, verapamil
3[b]	f	64	49	6	2.4	2.3	62	75	Chronic pyelonephritis	Methylprednisolon, metoprolol, benzbromaron
4	m	35	59	3	1.3	1.1	73	41	Polycystic kidney degeneration	Torasemide, metoprolol, nitrendipin, benzbromaron
5	m	66	64	2	1.9	1.6	65	47	Alport syndrome	Torasemide, metoprolol, nitrendipin, benzbromaron
6	f	44	86	3	1.2	1.5	53	48	Systemic lupus erythematosus	Benuzepril
7	m	39	60	3	1.0	0.9	38	35	Interstitial glomerulonephritis	Furosemide
8	m	42	73	2	1.6	1.7	58	53	Interstitial glomerulonephritis	Methylprednisolon, benazepril, moxonidine, metoprolol
9	f	42	73	4	0.7	0.7	22	26	Chronic pyelonephritis	Metoprolol, ranitidine
10	f	24	90	3	1.0	1.0	51	35	Chronic pyelonephritis	Furosemide, methylprednisolon, perindoprile, metoprolol
Mean				3.3	1.4	1.3	54	44		
SD				1.2	0.6	0.6	24	19		

[a]Values after 14 days of SJW treatment.
[b]Patients without mycophenolate mofetil comedication.

Table 2. Pharmacokinetic parameters of TAC and MPA acid with and without comedication with SJW extract

	AUC_1	AUC_2*	C_{max1}	C_{max2}*	t_{max1}	t_{max2}	$C_{trough1}$	$C_{trough2}$*	$C_{trough3}$*
TAC ($n=10$)									
	(ng/h/ml)		(ng/ml)		(hours)		(ng/ml)		
Median	180	75.9	23.0	12.7	1.5	1.3	10.8	3.8	7.6
25 percentile	144	57.4	17.0	9.5	1.0	1.0	8.5	2.9	5.6
75 percentile	202	99.3	28.3	16.6	2.3	1.5	12.9	4.6	10.8
P	0.005		0.005		0.09		0.005	0.005	0.03
MPA ($n=8$)									
	(μg/h/ml)		(μg/ml)		(hours)		(μg/ml)		
Median	69.9	73.2	19.7	19.8	0.5	0.5	2.9	4.7	4.1
25 percentile	56.0	54.8	17.9	14.2	0.5	0.5	2.6	1.9	1.5
75 percentile	81.7	86.6	24.4	24.1	0.9	1.0	6.0	5.8	5.3
P	0.3		0.4		0.3		0.7	0.5	0.9

*Values corrected for TAC dose.

treatment (Figure 1A). In order to achieve sufficient immunosuppression, the TAC dose had to be adjusted in all 10 patients, from a median of 4.5 mg/day to 8.0 mg/day. TAC trough levels, corrected for dose, decreased from a median 10.8 ng/ml before SJW administration to 3.8 ng/ml after 2 weeks of combination treatment (Table 2, Figure 2). Two weeks after discontinuation of SJW treatment, trough levels increased again to 7.6 ng/ml and patients returned to their previous dose ~4 weeks after the end of the study.

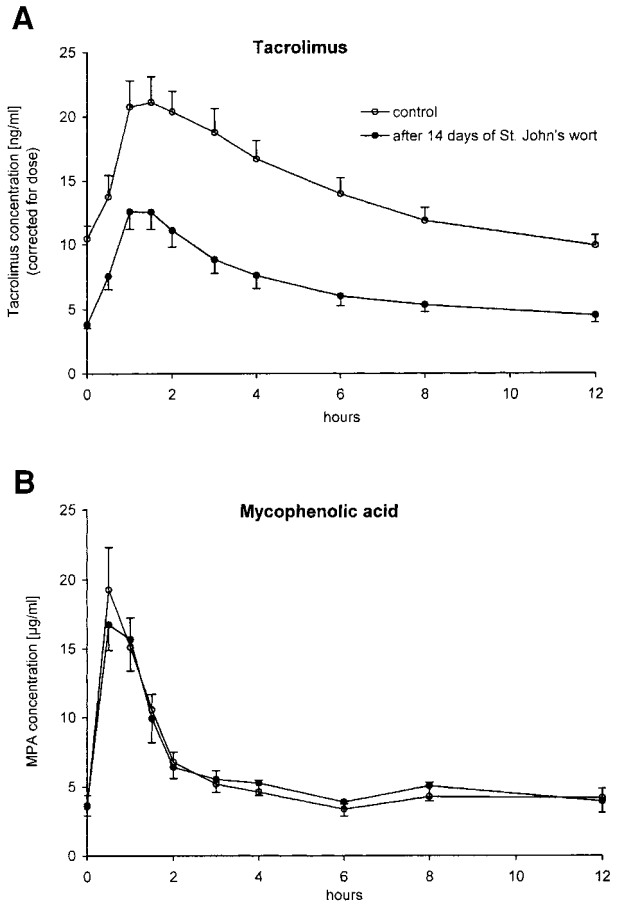

Fig. 1. (**A**) Effect of SJW co-administration on the blood concentrations of TAC. Blood concentrations obtained under SJW treatment have been corrected for the TAC dose administered on the day of the kinetic measurements. Values represent the mean ± SEM of 10 patients. (**B**) Effect of SJW co-administration on the plasma concentrations of MPA.Values represent the mean ± SEM of eight patients.

Mycophenolic acid

MPA pharmacokinetic parameters were not affected by co-administration of SJW (Table 2, Figure 1B).

Allograft function

Renal function remained stable during SJW treatment as indicated by creatinine and urea concentrations (Table 1).

Discussion

The reduced bioavailability for a number of orally dosed drugs that has been observed as a result of

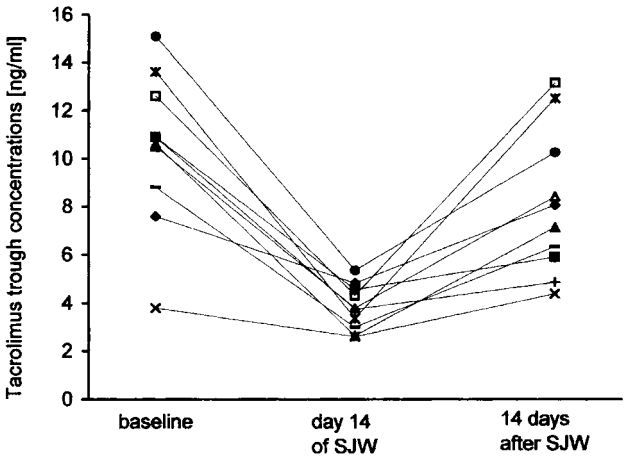

Fig. 2. Individual, dose-corrected TAC through concentrations before, during, and after SJW treatment.

comedication with SJW [3–7] can be explained by an induction of drug metabolizing enzymes (CYP3A) and drug transporters (P-gp) via the PXR receptor, which is caused by certain constituents of SJW extracts [8]. Induction of P-gp expression and activity by SJW has been shown *in vitro* and *in vivo* [9,10], and increased CYP3A activity measured as urinary excretion of 6β-hydroxycortisol has been found in healthy volunteers treated with SJW extract [11,12]. While presumably both mechanisms play a role in the observed interaction, their relative contribution to the overall effect can vary between different drugs, individuals and disease states. TAC undergoes extensive hepatic metabolism by cytochrome P-450 enzymes, mainly CYP3A4, and is also a substrate for P-gp [13]. Presumably, SJW influenced the TAC pharmacokinetics through induction of both mechanisms; however, relative contributions cannot be differentiated in this study. The majority of MPA is conjugated to D-glucuronic acid and excreted in the urine, and only a small amount of the drug is metabolized by CYP enzymes. An involvement of transmembrane transporters such as P-gp in the disposition of MPA has not been shown. The fact that induction of CYP3A4 and P-gp by SJW extract had no effect on the pharmacokinetics of MPA is consistent with a limited contribution of the enzyme and the transporter in MPA biotransformation.

In summary, SJW treatment resulted in a dramatic decrease ($>50\%$) in the bioavailability of TAC. Dose adjustments were indicted and resulted in stable renal function and no acute rejection episode. As a conclusion, co-administration of SJW extract with TAC should be avoided, especially in self-medication. If SJW is still the antidepressant of choice, patients need to be closely monitored and dose adjustments of TAC have to be made accordingly.

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