Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients

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Aim This study investigated the effects of St John's wort extract (SJW) on the pharmacokinetics and metabolism of the immunosuppressant cyclosporin A (CSA).
Methods In an open-label study, 11 renal transplant patients received 600 mg SJW extract daily for 14 days in addition to their regular regimen of CSA. Blood concentrations of CSA and its metabolites AM1, AM1C, AM9, AM19, and AM4N were measured by HPLC.
Results After 2 weeks of SJW coadministration, dose-corrected AUC_{0-12}, C_{max} and C_{trough} values for CSA decreased significantly by 46% [geometric mean ratio baseline/SJW (95% CI): 1.83 (1.63–2.05)], 42% [1.72 (1.42–2.08)], and 41% [1.70 (1.17–2.47)], respectively. CSA doses were increased from a median of 2.7 mg day^{-1} kg^{-1} at baseline to 4.2 mg day^{-1} kg^{-1} at day 15, with the first dose adjustment required only 3 days after initiation of SJW treatment. Additionally, the metabolite pattern of CSA was substantially altered during SJW treatment. Whereas dose-corrected AUC values for AM1, AM1c and AM4N significantly decreased by 59%, 61%, and 23% compared with baseline, AUC values for AM9 and AM19 were unchanged. Following the increase in CSA dose, observed AUC and C_{max} values for AM9, AM19, and AM4N increased by 20–51% and 43–90%, respectively.
Conclusion Administration of SJW extract to patients receiving CSA treatment resulted in a rapid and significant reduction of plasma CSA concentrations. Additionally, the substantial alterations in CSA metabolite kinetics observed may affect the toxicity profile of the drug.

Keywords: cyclosporin A, drug interaction, metabolism, patients, pharmacokinetics, St John's wort

Introduction

St John's wort (SJW, *Hypericum perforatum*) extracts are frequently used for the treatment of mild to moderate depression. Chronic use of SJW reduces the bioavailability of a number of drugs, including the cardiac glycoside digoxin [1], the HIV protease inhibitor indinavir [2], the antidepressant amitriptyline [3], and the immunosuppressant cyclosporin A (CSA). Several cases of acute heart, liver, and kidney transplant rejections due to decreased CSA blood levels during coadministration of SJW have been reported [4–9].

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CSA is the standard immunosuppressant in the prevention of allograft rejection after kidney, liver, heart, and bone marrow transplantations and is also used in the treatment of various autoimmune diseases. Frequently, CSA is administered in combination with steroids, azathioprin, or mycophenolic acid [10]. The drug undergoes extensive biotransformation by cytochrome P450 enzymes (CYP) to more than 30 metabolites that differ in their therapeutic activity and toxicity [11–13]. Metabolic alteration of single functional groups yields the primary metabolites AM1 (hydroxylated at amino acid 1), AM9 (hydroxylated at amino acid 9), and AM4N (N-demethylated at amino acid 4). These are subject to further biotransformation yielding AM1c (cyclized AM1) and AM19 (hydroxylated at amino acids 1 and 9) as the quantitatively most important secondary metabolites [12]. The main enzyme in CSA metabolism is CYP3A4 [14], but other isoforms may be involved [15–17]. CSA is also

a substrate for the MDR1-transporter P-glycoprotein (P-gp) [18–20].

Induction of intestinal P-gp can decrease drug absorption by stimulating the active efflux of the drug back into the intestinal lumen [21, 22], an effect that was first proposed to explain the SJW–digoxin interaction [1]. Decreased systemic availability and plasma drug concentrations can also be the result of intestinal and hepatic induction of CYP enzymes. SJW extracts contain a variety of compounds [23], with hypericin, pseudohypericin, and hyperforin among those presumed responsible for its antidepressive activity [24, 25]. Hyperforin has been shown to strongly activate the PXR receptor, which is involved in the regulation of CYP3A and P-gp expression [26, 27].

The present study investigated the effects of 14 days of concomitant treatment with 600 mg hypericum extract per day on the pharmacokinetics of CSA and its primary (AM1, AM9, AM4N) and major secondary (AM1c, AM19) metabolites in renal transplant patients.

Methods

Patients

Eleven renal transplant patients (9M, 2F) at least 2 years after surgery were enrolled and all patients completed the study. Inclusion criteria were: stable CSA dose for 3 months prior to enrolment, trough blood concentrations in the range 100–150 μg l^{-1} verified by two consecutive measurements, and stable allograft function (creatinine clearance >30 ml min^{-1}). Patients underwent general blood and urine analysis, ECG, and physical examination prior to enrolment. Detailed patient characteristics are reported in Table 1. Dietary restrictions included caffeine, alcohol and grapefruit juice. Co-medications remained unchanged during the course of the study, which was approved by the ethics committee of the University Medical Centre Charité, Humboldt University of Berlin. All patients gave their written informed consent.

Study design

In an open-label design, patients received 600 mg SJW extract (two coated tablets Jarsin300™; Lichtwer Pharma, Berlin, Germany) once daily, together with the CSA morning dose for 14 days in addition to their normal regimen of CSA (Sandimmun® Optoral; Novartis Pharma, Nürnberg, Germany, which contained all-rac-alpha-tocopherol as an antioxidant). One tablet of Jarsin300 consisted of 300 mg of a dried methanolic extract of SJW containing hypericin, pseudohypericin, and hyperforin [3]. Owing to safety considerations in response to case reports on serious CSA and SJW drug interactions [4–9], the selected dose of SJW extract (600 mg day^{-1}) was below the recommended therapeutic dose for this preparation (900 mg day^{-1}). The pharmaco-

Table 1 Characteristics of renal transplant patients participating in the study.

No.	Sex	Age	Weight (kg)	Years post-transplant	Creatinine (mg dl^{-1}) Baseline	Creatinine (mg dl^{-1}) SJW*	Urea (mg dl^{-1}) Baseline	Urea (mg dl^{-1}) SJW*	Baseline CSA dose (mg kg^{-1} day^{-1})	Co-medication
1	M	34	74	11	1.1	1.1	55	44	3.4	Methylprednisolon, nisoldipin, atenolol
2	M	46	86	10	1.3	1.4	70	70	2.5	Methylprednisolon, furosemide, cerivastatin, azathioprine
3	M	42	81	13	1.4	1.5	75	69	2.7	Methylprednisolon, metoprolol, benazepril, benzbromaron
4	F	48	77	10	0.7	0.8	44	32	2.0	Methylprednisolon, felodipin, losartan
5	F	58	64	10	1.4	1.3	68	74	2.8	Methylprednisolon, nitrendipin, benzbromaron
6	M	50	73	16	1.5	1.7	54	61	2.3	Methylprednisolon, amlodipin, allopurinol
7	M	35	63	11	2.1	2.4	75	74	3.2	Methylprednisolon, nitrendipin
8	M	54	80	6	1.5	1.3	58	53	3.7	Methylprednisolon, nitrendipin, celiprolol, cerivastatin, ranitidin, benzbromaron
9	M	59	83	9	1.4	1.4	59	53	4.2	Methylprednisolon, amlodipin, doxazosin, benzbromaron, mycophenolate-mofetil, furosemide
10	M	52	85	6	2.0	2.2	77	69	1.9	Methylprednisolon, nitrendipin, celiprolol
11	M	39	95	12	2.1	2.0	77	61	2.1	Methylprednisolon, amlodipin, cerivastatin, doxazosin, piretanid
Mean				10.4	1.5	1.6	65	60	2.8	
s.d.				2.9	0.4	0.5	11	13	0.7	

*Values after 14 days of St John's wort treatment.

kinetics of CSA and its metabolites AM1, AM9, AM4N, AM1c and AM19 were measured on the day before initiation of SJW treatment (study day 1) and after 14 days of SJW treatment (study day 15). At sampling times of 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h post administration of CSA, venous blood samples of 5 ml were drawn into EDTA-coated tubes. Trough concentrations of CSA were also determined on days 4, 8, 11, 18, 22 and 29, and doses were adjusted as required based on trough concentrations to assure CSA blood concentrations in the therapeutic range of 70–150 μg l^{-1}. Doses were kept stable at least 2 days prior to the second CSA kinetic measurements to ensure steady-state conditions.

Sample analysis

CSA and its metabolites AM1, AM9, AM4N, AM1c and AM19 were quantified using a modification of the HPLC method by Christians *et al*. [28]. Briefly, 0.5 ml blood was spiked with the internal standard (cyclosporin D) and loaded onto a solid-phase extraction cartridge (Baker-Bond C8; J. T. Baker, Phillipsburg, NJ, USA). The samples were washed with 30% acetonitrile in water and n-hexane and eluted with dichloromethane. The solvent was evaporated and samples were reconstituted in 50% acetonitrile in water. Analysis was performed using a Shimadzu HPLC system (Duisburg, Germany) consisting of two pumps LC-10AS, an automatic sampler SIL-10A, and a dual-wavelength u.v. detector SPD-10A set at 210 nm. The compounds were separated by gradient elution at 60°C on a Hypersil ODS column (5 μm, 250 × 4.6 mm i.d.; Optilab, Berlin, Germany) with a guard column (5 μm, 10 × 4.6 mm i.d.). Mobile phase A consisted of 10% acetonitrile and 0.01% phosphoric acid in water and mobile phase B consisted of 90% acetonitrile and 0.01% phosphoric acid in water. Gradient elution started at 50% of B for 10 min, was increased to 75% at 35 min, kept constant until 40 min, was increased to 100% at 50 min and reduced to 50% at 52 min. Total run time was 60 min at a flow rate of 1.0 ml min^{-1}. The compounds were quantified using their peak height ratio to an internal standard based on the calibration curve of CSA. Metabolites were identified by comparison of their retention times with reference standards (Dade Behring, Deerfield, IL, USA) and bile extract. The assay was linear up to 2000 μg l^{-1}. Intra- and inter-assay coefficients of variation ranged from 3.2% to 14.1% and from 2.4% to 12.8%, respectively. The lower limit of quantification was 20 μg l^{-1}. CSA trough concentrations were determined by homogeneous enzyme immunoassay (Emit™; Dade Behring, Deerfield, IL, USA) using a COBAS MIRA S analyser (Hoffmann-La Roche AG, Basel, Switzerland).

Pharmacokinetics

Steady-state pharmacokinetics of CSA were characterized by the area under the plasma concentration–time curve within one dosing interval (AUC_{0-12}), the drug concentration at the end of one dosing interval (C_{trough}), peak concentration in plasma (C_{max}) and time to reach C_{max} (t_{max}). AUC_{0-12} was calculated using the linear trapezoidal rule (WinNonLin Pro 1.5; Pharsight Corp., Mountain View, CA, USA). In order to account for the dose adjustments, values of AUC, C_{max}, and C_{trough} were corrected by multiplication with the ratio of baseline dose/dose on SJW.

Statistical analysis

The primary aim of the study was to evaluate the influence of SJW co-medication on the steady-state AUC_{0-12} of CSA. Considering a 30% difference in CSA AUC_{0-12} to be clinically relevant, a necessary sample size of 11 subjects was calculated with a paired two-sided *t*-test with a type-I error of 0.05 and a type-II error of 0.20. Calculations were based on the known variability in the AUC_{0-12} of CSA in kidney transplant patients of 5069 ± 1480 μg h^{-1} l^{-1} (mean ± s.d.) [29]. Values were log-transformed and baseline and SJW data were compared using a two-sided *t*-test (SPSS 10.0; SPSS Inc., Chicago, IL, USA).

Results

CSA pharmacokinetics

In order to maintain CSA blood concentrations in the therapeutic range (70–150 μg l^{-1}), median daily CSA doses were increased from 2.7 mg day^{-1} kg^{-1} at baseline to 4.2 mg day^{-1} kg^{-1} after 10 days of SJW treatment on study day 12 (Figure 1). All 11 patients required a first CSA dose adjustment 3 days after the initiation of SJW co-medication. Despite dose adjustments, the CSA pharmacokinetics resulting on day 15 did not quite reach pretreatment values (Table 2, Figure 2). After discontinuation of SJW treatment, CSA doses had to be decreased. However, the median dose was still 3.2 mg day^{-1} kg^{-1} on study day 30, and baseline doses were reached only in three patients (Figure 1).

The median dose-corrected values for CSA after 2 weeks of SJW treatment showed a significant decrease in AUC_{0-12}, C_{max}, and C_{trough} by 41% to 45% (Table 2, Figure 2). Despite subtherapeutic SJW doses, the effect was evident in all 11 patients, with the reduction in CSA AUC_{0-12} ranging between 30% and 60%.

Table 2 Pharmacokinetic parameters for CSA at baseline and after 14 days of SJW co-medication (600 mg day^{-1}).

	Baseline	*SJW*[†] *observed data*	*SJWc*[‡] *dose corrected data*	*Ratio*[§] *(95% CI)*
AUC_{0-12} (μg h^{-1} l^{-1})[¶]	3319 (3034–3606)	2832 (2456–3824)⋆	1818 (1447–2274)⋆⋆	1.83 (1.63–2.05)
C_{max} (μg l^{-1})	1077 (955–1275)	976 (697–1292)	627 (503–831)⋆⋆	1.72 (1.42–2.08)
C_{trough} (μg l^{-1})	93 (74–121)	70 (53–102)	55 (44–70)⋆	1.70 (1.17–2.47)
t_{max} (h)[††]	1.0 (1.0–1.5)	1.0 (1.0–1.5)		

During SJW treatment, CSA doses were successively increased to compensate for decreasing CSA blood concentrations. [†]Parameters after 14 days of SJW treatment derived from observed data (not corrected for CSA dose). [‡]Parameters after 14 days of SJW treatment derived from data corrected for CSA dose. [§]Geometric mean ratios between baseline values and dose corrected data, with 95% confidence intervals in parentheses. [¶]Geometric means with 25th and 75th percentiles in parentheses. [††]Median with 25th and 75th percentiles in parentheses. ⋆$P < 0.05$; ⋆⋆$P < 0.005$ (two-way *t*-test compared with baseline).

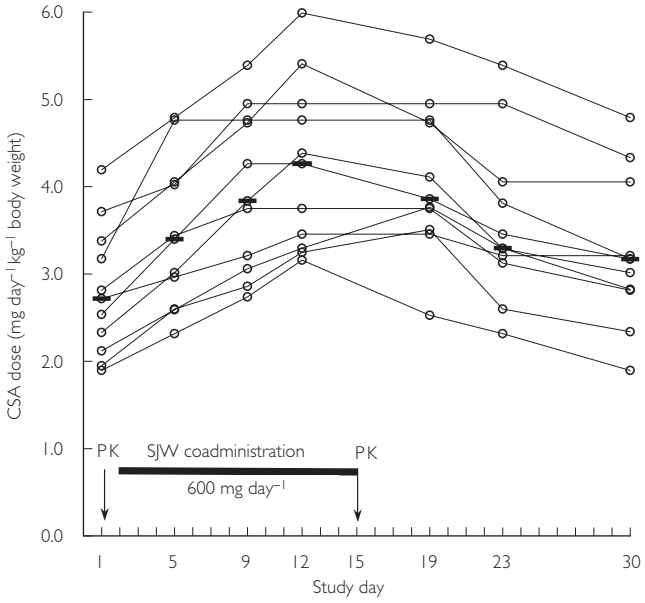

Figure 1 Individual CSA doses required to maintain sufficient immunosuppression during SJW co-medication. CSA trough concentrations were measured on study days 4, 8, 11, 18, 22 and 29, with dose adjustments effective the following day (ie study days 5, 9, 12, 19, 23 and 30). SJW extract was coadministered between day 2 and day 15 (black bar). CSA pharmacokinetics were measured on study days 1 and 15 (arrows). Horizontal bars indicate the median dose.

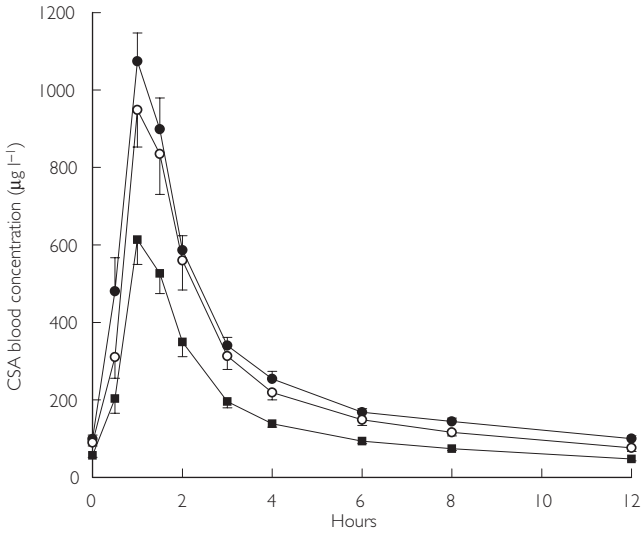

Figure 2 Blood concentrations of CSA in 11 renal transplant patients at baseline (●), after 14 days of SJW treatment with a compensatory increase in CSA dose (○), and after 14 days of SJW treatment with data corrected for CSA dose (■). Values are means ± s.e.m.

CSA metabolite pharmacokinetics

Data corrected for CSA dose Dose-corrected: AUC_{0-12}, C_{max}, and C_{trough} values for AM1 and AM1c were significantly reduced by approximately 60%, an effect larger than the one observed for the parent compound. In contrast, the metabolites AM9 and AM19 remained unaffected by SJW treatment when blood concentrations were corrected for CSA dose. AM4N showed decreased dose-corrected AUC and C_{trough} values (−23% and −42%, respectively), whereas C_{max} was unchanged (Table 3, Figure 3a).

Observed uncorrected data: At increased CSA doses, the AUC_{0-12} and C_{max} values for AM1 and AM1c remained 35% lower than those at baseline, and C_{trough} values were decreased by more than 50% (Table 3, Figure 3b). The AUC values for AM9, AM19, and AM4N increased significantly by 47%, 51%, and 20%, respectively. Corresponding C_{max} values increased significantly by 57%, 90%, and 43%, respectively (Table 3, Figure 3b).

As a consequence of those differential effects on individual metabolic pathways, the pattern of CSA metabolism was considerably altered during SJW treatment, particularly around t_{max} (1–2 h). Whereas AM1 followed by AM9 showed the highest C_{max} values and metabolic ratios at baseline, this order was reversed after 2 weeks of SJW treatment (Table 3, Figures 3b and 4a). Additionally, exposure to AM19 and AM4N increased significantly,

Table 3 Pharmacokinetic parameters for CSA metabolites at baseline and after 14 days of SJW co-medication (600 mg day^{-1}).

	AUC_{0-12} ($\mu g\ h^{-1}\ l^{-1}$)	C_{max} ($\mu g\ l^{-1}$)	C_{trough} ($\mu g\ l^{-1}$)
AM1			
Baseline	11 901 (10 608–14 230)	1 534 (1284–1959)	777 (677–820)
SJW[†]	7 558 (6950–8596)**	1 105 (863–1329)*	400 (339–503)**
SJWc[‡]	4 852 (3909–5989)**	709 (599–816)**	322 (258–391)**
Ratio (95% CI)[§]	2.45 (2.17–2.77)	2.16 (1.56–3.00)	2.41 (2.10–2.77)
AM1c			
Baseline	1 355 (1122–1598)	188 (165–210)	87 (72–120)
SJW	823 (627–1191)**	119 (93–167)*	38 (25–83)*
SJWc	529 (392–761)**	76 (52–106)**	31 (22–57)**
Ratio (95% CI)	2.56 (1.92–3.42)	2.47 (1.76–3.45)	2.78 (1.69–4.58)
AM9			
Baseline	3 716 (2635–5295)	806 (580–1200)	114 (106–160)
SJW	5 460 (5071–6672)**	1 269 (925–1560)**	149 (129–156)
SJWc	3 506 (2988–4448)	815 (587–1054)	114 (87–151)
Ratio (95% CI)	1.06 (0.94–1.20)	0.99 (0.75–1.30)	1.00 (0.79–1.28)
AM19			
Baseline	781 (604–1072)	153 (119–239)	38 (20–62)[¶]
SJW	1 180 (1052–1552)**	291 (177–387)**	35 (18–55)
SJWc	758 (592–899)	187 (102–258)	24 (11–36)**
Ratio (95% CI)	1.03 (0.92–1.15)	0.82 (0.65–1.04)	1.59 (1.32–1.90)
AM4N			
Baseline	1 146 (940–1603)	312 (211–458)	46 (28–65)[¶]
SJW	1 374 (1237–1681)*	447 (289–607)**	41 (24–61)
SJWc	882 (737–1177)**	287 (173–415)	27 (17–41)**
Ratio (95% CI)	1.30 (1.16–1.46)	0.92 (0.85–1.39)	1.72 (1.39–2.12)

Geometric means with 25th and 75th percentiles in parentheses. During SJW treatment, CSA doses were successively increased to compensate for decreasing CSA blood concentrations. [†]Parameters after 14 days of SJW treatment derived from observed data (not corrected for CSA dose). [‡]Parameters after 14 days of SJW treatment derived from data corrected for CSA dose. [§]Geometric mean ratios between baseline values and dose corrected data, with 95% confidence intervals in parentheses. [¶]$n = 10$, one patient did not show measurable AM19 and AM4N blood concentrations. *$P < 0.05$; **$P < 0.005$ (two-way t-test compared with baseline).

whereas the AM1c metabolic ratio was decreased (Figure 4a). Trough concentrations at 12 h post dose showed less pronounced effects. However, AM1 metabolic ratios still tended to be lower and AM9/CSA ratios significantly higher than the corresponding baseline values (Figure 4b).

Allograft function

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

Discussion

Although several case reports have described serious interactions between CSA and SJW [4–8], detailed pharmacokinetic data have not been available until now. The present study has demonstrated that co-medication with SJW extract rapidly (3 days after initiation of treatment) and substantially (more than a 40% decrease in AUC_{0-12}) altered the pharmacokinetics of CSA in all 11 patients, requiring repeated CSA dose adjustments to ensure continued therapeutic activity of the immunosuppressant (Figure 1). Although the SJW dose used in this study (600 mg day^{-1}) was below that recommended for this formulation (900 mg day^{-1}), the CSA dose had to be increased by 60%. The reversal of the effect after discontinuation of SJW co-medication took longer than 2 weeks in 8/11 patients.

The reduced plasma concentrations of several orally administered drugs that have been observed after co-medication with SJW [1–3] can be explained by induction of drug-metabolizing enzymes (CYP3A) and/or drug transporters (P-gp) via the PXR receptor [21, 22, 26]. CSA undergoes extensive hepatic metabolism by cytochrome P-450 enzymes, mainly CYP3A4 [11, 12, 14] and is also a substrate for P-gp [18–20]. Although more than 80% of CSA metabolism is attributed to CYP3A4 [14], CYP3A5 has also been shown to metabolize CSA [16], and there is some evidence that the

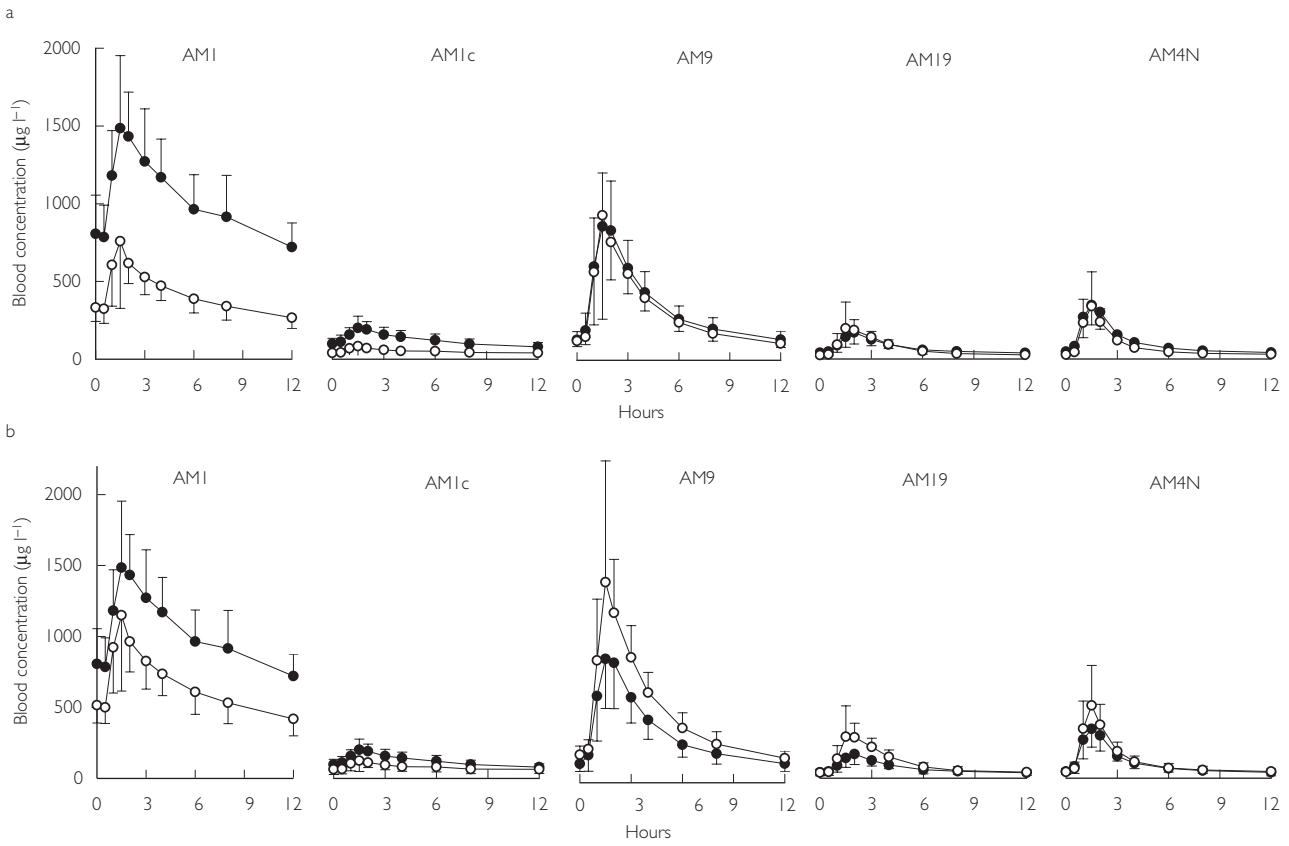

Figure 3 Blood concentrations of CSA metabolites in 11 renal transplant patients at baseline (●) and after 14 days of SJW treatment (○). Values are means ± s.d. (a) Data corrected for CSA dose. (b) Observed uncorrected data.

formation of cyclic metabolites (AM1c, AM1c9) may be mediated by 3-methylcholanthrene-inducible CYP isoforms such as CYP1A1 or CYP1A2 [15, 17]. Furthermore, the effects observed with different preparations of SJW may vary greatly, depending on the composition of the individual plant extract.

SJW treatment caused differential effects on the pharmacokinetics of CSA metabolites. The profiles of the five metabolites quantified in this study fell into two distinct groups. Thus, AM1 and AM1c showed markedly reduced blood concentrations in all 11 patients even after CSA dose adjustment, whereas the C_{max} values of AM9, AM19, and AM4N were unchanged after correction for CSA dose. A similar pattern, although in reverse direction, was previously seen with the calcium antagonist diltiazem, which caused an increase in CSA and AM1 blood concentrations, whereas AM9 levels remained unchanged [30]. CSA and its metabolites are mainly eliminated via bile [31], with 96% of an oral dose recovered in faeces and less than 0.1% of the parent drug eliminated unchanged [32]. It has been shown that the biliary excretion of CSA in P-gp knockout mice is reduced to approximately 30% of that in wild-type animals [33]. It can be hypothesized that the induction of P-gp by SJW results in enhanced biliary excretion of those CSA metabolites with higher affinities for P-gp, and they would also be less likely to be reabsorbed from the intestine. As a result, the enterohepatic cycle would be interrupted and blood concentrations of P-gp substrates would decrease. Poor P-gp substrates, on the other hand, would not be affected by P-gp induction. The observed increase in blood concentrations of AM9, AM19, and AM4N may be the result of CYP3A induction, an effect that could be masked for AM1 and AM1c by their enhanced elimination. *In vitro* studies characterizing the CSA interaction metabolites with P-gp would be valuable to explain the differential effects of SJW on CSA metabolite kinetics. However, the lack of availability of authentic standards of CSA metabolites limits such studies. Additionally, acute inhibition of CYP3A4, CYP2D6, CYP1A2, and CYP2C9 activity by SJW constituents has been shown *in vitro* [34]. Considering the long half-lives of the SJW constituents hypericin, pseudohypericin and hyperforin (42 h, 23 h, and 16 h, respectively) [3, 35], such inhibitory effects on hepatic or intestinal CYP activity may also contribute to the interactions of SJW with several drugs.

Although therapeutic CSA concentrations could be

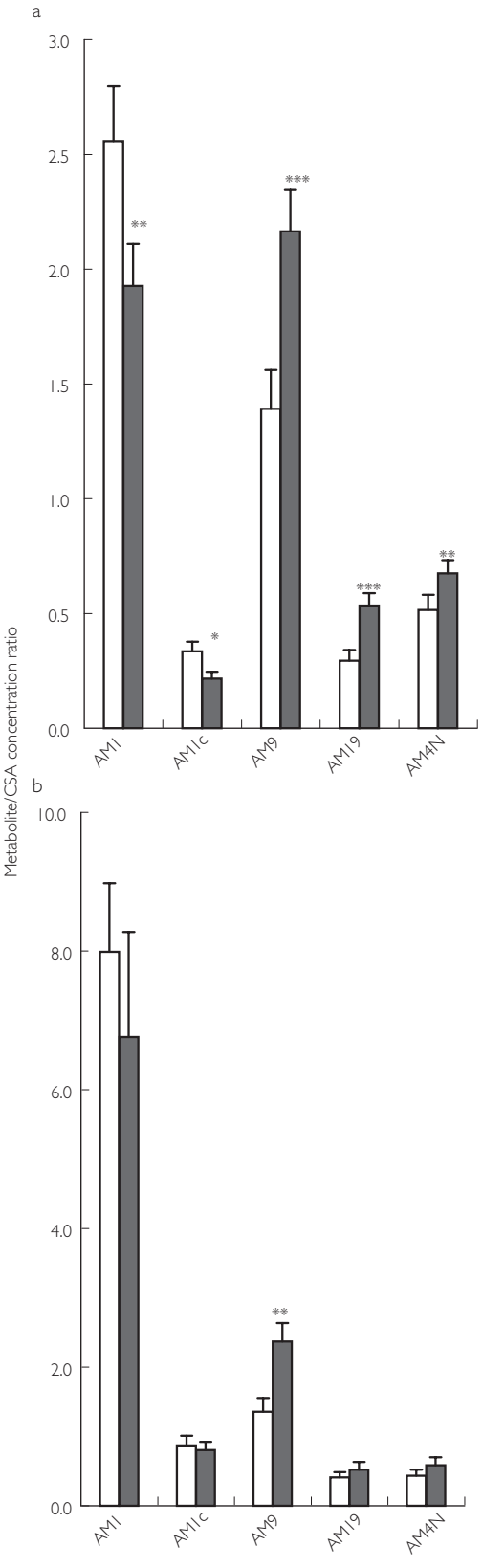

Figure 4 Observed metabolite/CSA concentration ratios in 11 renal transplant patients at baseline (□) and after 14 days of SJW treatment (■). Values are means + s.e.m. (a) At C_{max} (2 h after CSA dose). (b) At C_{trough} (12 h after CSA dose). ⋆$P < 0.05$; ⋆⋆$P < 0.01$; ⋆⋆⋆$P < 0.005$ (two-way t-test compared with baseline).

maintained under SJW co-medication by appropriate dose adjustments, the resulting pattern of CSA metabolites was substantially altered. Whereas baseline metabolite patterns were consistent with previously reported findings [36], SJW treatment resulted in increased exposure to AM9, AM19, and AM4N, particularly around t_{max}. High blood concentrations of total CSA metabolites have been repeatedly associated with CSA nephrotoxicity [37–39], and elevated AM1 concentrations have been reported to coincide with severe CNS toxicity symptoms [40]. In the same study, rejection episodes after kidney transplants were associated with low AM1 and AM9 blood concentrations, suggesting that CSA metabolites may contribute to the immunosuppressant activity of the drug [40]. These findings indicate that the influence of chronic SJW coadministration may go beyond a decrease in CSA parent drug bioavailability, but could potentially lead to alterations in treatment efficacy and toxicity. In humans, CSA toxicity affects kidney, liver, pancreas, and CNS, with nephrotoxicity presenting the major limitation in clinical use [41]. The molecular basis of CSA toxicity remains unclear, but proposed mechanisms include a modulation of CYP patterns in liver and kidney, covalent binding to macromolecules, alterations in endotheline production, as well as the occurrence of alternative CSA metabolic pathways [42, 43]. In rat or cell culture models, CSA metabolites show less toxicity than the parent compound [44, 45]. However, synergistic effects between CSA and its metabolites or between different metabolites have been proposed [46].

In summary, administration of SJW extract to renal transplant patients being treated with a stable CSA regimen resulted in a rapid and significant decrease in CSA blood concentrations associated with the risk of inadequate immunosuppression. In order to compensate for the decrease in AUC, CSA doses had to be increased by 60%. Additionally, the metabolite pattern of CSA was substantially altered during SJW co-medication. In light of the fact that the molecular mechanism of CSA toxicity and the role of individual CSA metabolites in this process are as yet unknown, an effect of chronic SJW treatment on the toxicity profile of CSA cannot be excluded. Coadministration of SJW extract to patients during CSA therapy appears to be associated with a substantial risk of therapy failure and a considerable increase in treatment costs and therefore should be avoided.

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