PHARMACOKINETICS AND DRUG DISPOSITION

Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics

Objectives: **Constituents of St John's wort (SJW) in vivo induce the cytochrome P450 (CYP) isozymes 3A4, 2C9, and 2C19 but in vitro were shown to inhibit them. This study investigates both short- and long-term effects of SJW on the antifungal voriconazole, which is metabolized by these enzymes.**

Methods: **In a controlled, open-label study, single oral doses of 400 mg voriconazole were administered to 16 healthy men stratified for *CYP2C19* genotype before and on day 1 and day 15 of concomitant SJW intake (300 mg LI 160 3 times daily). Plasma and urine concentrations of voriconazole were determined by liquid chromatography with mass-spectrometric detection.**

Results: **During the initial 10 hours of the first day of SJW administration, the area under the voriconazole plasma concentration–time curve was increased by 22% compared with control (15.5 ± 6.84 h · μg/mL versus 12.7 ± 4.16 h · μg/mL, $P = .02$). After 15 days of SJW intake, the area under the plasma concentration–time curve from hour 0 to infinity was reduced by 59% compared with control (9.63 ± 6.03 h · μg/mL versus 23.5 ± 15.6 h · μg/mL, $P = .0004$), with a corresponding increase in oral voriconazole clearance (CL/F) from 390 ± 192 to 952 ± 524 mL/min ($P = .0004$). The baseline CL/F of voriconazole and the absolute increase in CL/F were smaller in carriers of 1 or 2 deficient *CYP2C19*2* alleles compared with wild-type individuals ($P < .03$).**

Conclusions: **Coadministration of SJW leads to a short-term but clinically irrelevant increase followed by a prolonged extensive reduction in voriconazole exposure. SJW might put *CYP2C19* wild-type individuals at highest risk for potential voriconazole treatment failure. (Clin Pharmacol Ther 2005;78:25-33.)**

Jens Rengelshausen, MD, Maria Banfield, Klaus-Dieter Riedel, MS, Jürgen Burhenne, PhD, Johanna Weiss, PhD, Torben Thomsen, MD, Ingeborg Walter-Sack, MD, Walter E. Haefeli, MD, and Gerd Mikus, MD

Heidelberg and Mönchengladbach, Germany

Extracts of St John's wort (*Hypericum perforatum* L) (SJW) are widely used as over-the-counter remedies for the treatment of mild to moderate depressive disorders.[1]

From the Department of Internal Medicine VI, Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Heidelberg, and Pharm PlanNet, Mönchengladbach.

Received for publication Jan 12, 2005; accepted April 1, 2005.

Reprint requests: Gerd Mikus, MD, Department of Internal Medicine VI, Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany.

E-mail: *gerd_mikus@med.uni-heidelberg.de*

0009-9236/$30.00

doi:10.1016/j.clpt.2005.01.024

Coadministration of SJW was followed by clinically relevant treatment failures of drugs such as cyclosporine (INN, ciclosporin) or oral contraceptives, resulting in acute heart transplant rejections[2] or unwanted pregnancies.[3] Subsequent clinical studies confirmed that coadministration of SJW extensively reduces the plasma concentrations of drugs such as digoxin,[4] indinavir,[5] cyclosporine,[6,7] tacrolimus,[8,9] warfarin,[10] omeprazole,[11] verapamil,[12] and imatinib.[13] Most of these drugs are metabolized by cytochrome P450 (CYP) 3A4 or transported by P-glycoprotein (or both). As the basis for these interactions, SJW was shown to induce the expression of intestinal and hepatic CYP3A4, as well as intestinal P-glycoprotein, in humans.[14]

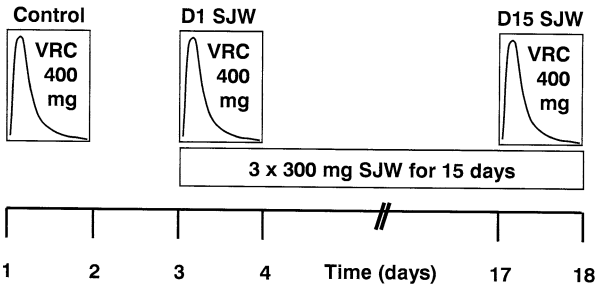

Fig 1. Fixed-dose study schedule according to controlled, open-label design. Single oral doses of 400 mg voriconazole (VRC) were administered during the 3 study parts. In addition, 300 mg St John's wort (SJW) (LI 160) was given 3 times daily for 15 days from study day 3 (D1 SJW) until study day 17 (D15 SJW).

The extracts of SJW contain different groups of compounds such as hypericin, hyperforin, and flavonoids.[15] These compounds vary widely in their content between different preparations.[16] In clinical studies the content of hyperforin determined the extent of the interaction with digoxin[17] and cyclosporine.[18] These findings are in line with in vitro data showing a relevant increase in messenger ribonucleic acid and protein of CYP3A4 and CYP2C9 in cultured human hepatocytes after hyperforin treatment for 48 hours.[19] Hyperforin mediates the induction of CYP3A4 expression by high-affinity binding and subsequent activation of the pregnane X receptor (PXR).[20] In addition to the long-term inducing effect, hyperforin was shown to inhibit the activity of CYP isozymes 1A2, 2C9, 2C19, 2D6, and 3A4 in vitro when added to the culture medium for a short term.[21,22] Therefore the primary aim of this study was to investigate the short- and long-term effects of SJW on the pharmacokinetics of voriconazole.

The new triazole antifungal voriconazole is used for the treatment of severe fungal infections.[23] In immunocompromised patients with invasive aspergillosis, initial treatment with voriconazole led to improved survival rates compared with initial therapy with amphotericin B.[24] The extensive metabolism of voriconazole is primarily mediated by CYP2C19 and CYP3A4, as well as by CYP2C9 to a lesser extent.[25] Genetic polymorphisms of CYP2C19 influence the plasma concentrations of voriconazole, which are approximately 3 times higher in poor metabolizers compared with homozygous extensive metabolizers, with intermediate concentrations in heterozygous extensive metabolizers.[26] Poor metabolizers for CYP2C19 (3%-5% in white subjects) carry 2 defective alleles, of which the *CYP2C19*2* allele accounts for about 80% of mutated alleles.[27] With the use of mephenytoin as a test substance, SJW was shown to induce the activity of CYP2C19 in extensive metabolizers but not in poor metabolizers.[28] Therefore the secondary aim of this study was to investigate, in an exploratory way, the influence of the *CYP2C19* genotypes on the interaction between SJW and voriconazole.

METHODS

The study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg, Heidelberg, Germany, and was conducted at the Department of Internal Medicine VI, Clinical Pharmacology and Pharmacoepidemiology in accordance with the Declaration of Helsinki, as amended in Somerset West 1996, and the specific legal requirements in Germany.

Study population

Seventeen healthy, nonsmoking men participated in the study after they had been fully informed about the study and given written informed consent. None was receiving any other systemic drug treatment during the study, and systemic drug treatment had to be discontinued for at least 10 elimination half-lives of the respective compound. The participants were ascertained to be healthy by medical history, physical examination, laboratory screening including hematologic and biochemical blood tests, and a 12-lead electrocardiogram. The mean age, body weight, and body mass index ($\pm$ SD) were 27 $\pm$ 3.4 years, 79 $\pm$ 6.7 kg, and 24 $\pm$ 2.1 kg/m^2, respectively. Before inclusion into the study, the participants underwent genotyping for the *CYP2C19* alleles **2* and **3* and were grouped according to the following genotypes found: *CYP2C19* wild type (*CYP2C19*1/*1*, n = 9), *CYP2C19*1/*2* (n = 6), and *CYP2C19*2/*2* (n = 2). Individuals carrying the *CYP2C19*3* allele were not found in this study population. The values for age, body weight, and body mass index were not significantly different between the *CYP2C19* wild-type group and the combined *CYP2C19*1/*2* and **2/*2* group ($P > .15$).

Study design and procedures

According to a controlled, open-label, fixed-dose schedule design, each participant received a single oral dose of 400 mg voriconazole (2 VFEND 200-mg film tablets; Pfizer, Sandwich, Kent, United Kingdom) on study days 1, 3, and 17. In addition, each participant received 300 mg SJW extract LI 160 (Jarsin, 300 mg; Lichtwer Pharma, Berlin, Germany) orally 3 times daily (approximately every 8 hours) for 15 days from

study day 3 to 17 (Fig 1). The intake of SJW was monitored by an electronic device (MEMS V TrackCap; Aardex, Zug, Switzerland). On study days 3 and 17, SJW was ingested 60 minutes before voriconazole administration to reduce the probability of a galenic interaction. After an overnight fast from 12 hours before until 4 hours after voriconazole administration, each participant received a standard hospital lunch and dinner served 4 and 9 hours after voriconazole dosing. Alcoholic and caffeinated beverages were not allowed from 24 hours before study day 1 until study day 4 and from study day 16 until study day 18. During study days 1 to 18, beverages containing grapefruit juice had to be avoided. On study days 1, 3, and 17, venous blood samples (7.5 mL each) were collected through an intravenous catheter into heparinized tubes immediately before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 24 hours after the administration of voriconazole. The blood samples were immediately centrifuged (3000*g* for 10 minutes at 4°C), and separated plasma samples were stored at −20°C until analysis. After completely voiding the bladder immediately before voriconazole intake, the participants collected urine from 0 to 24 hours after voriconazole administration. After measurement of the urine volume, a 10-mL aliquot of each fraction was stored at −20°C until analysis.

Determination of voriconazole concentrations in plasma and urine

Voriconazole concentrations in plasma and urine were determined after solid-phase extraction on the basis of a previously described HPLC assay[29] and optimized by use of liquid chromatography with mass-spectrometric detection.

In brief, plasma and urine samples (500 μL of standards, controls, and unknown samples) were spiked with internal standard (UK-115,794) and 0.2-mol/L borate buffer (pH 9.0, 700 μL) was added. Buffered and vortexed samples were loaded onto conditioned C_{18} SPE columns (BondElut, 100 mg; Varian, Darmstadt, Germany) and washed with borate buffer and methanol/water (50:50) before being eluted with 1 mL of methanol/acetic acid mixture (99:1). The extracts were dried under streams of nitrogen, and the dried residues were reconstituted with mobile liquid chromatography phase, centrifuged, and analyzed by liquid chromatography–mass spectrometry. For mass selective detection, the liquid chromatography system consisted of a Luna C_{18} column (3 μm, 50 × 2.0 mm at 40°C) and an isocratic mobile phase with the use of 0.02-mol/L ammonia acetate including 0.1% acetic acid and acetonitrile (65:35 [vol/vol]) at a flow rate of 0.35 mL/min. The injection volume was 10 μL. An atmospheric pressure chemical ionization source (4.5 kV, 400°C) was used for ionization, and the mass spectrometer worked in the selected ion monitoring mode at mass-to-charge ratio (*m/z*) 350 (voriconazole) and *m/z* 348 (internal standard). The limit of quantification was 0.05 μg/mL, and the calibration ranged between 0.05 μg/mL and 10.0 μg/mL. Correlation coefficients were always $r^2 > 0.99$. The analytic methods were validated according to Food and Drug Administration validation guidelines and fulfilled the respective quality assurance requirements for accuracy and precision. For plasma, the precision of determination (coefficient of variation) was 9.5%, 7.0%, 9.2%, and 7.9% and the accuracy was 105.3%, 100.9%, 96.1%, and 96.8% at quality-control concentrations of 0.16, 0.38, 3.15, and 6.38 μg/mL, respectively. For urine, the precision of determination (coefficient of variation) was 4.8%, 6.1%, 2.7%, and 3.9% and the accuracy was 110.3%, 114.3%, 92.0%, and 93.2% at concentrations of 0.17, 0.43, 3.01, and 6.14 μg/mL, respectively.

Pharmacokinetic analysis

Noncompartmental analysis by use of WinNonlin 4.0 software (Pharsight, Mountain View, Calif) was performed to determine pharmacokinetic parameters of voriconazole. The peak plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were obtained directly from the raw data. The terminal plasma elimination half-life ($t_{½}$) was calculated as follows: $t_{½} = \ln 2/\lambda_z$, where λ_z represents the slope of the terminal part of the plasma concentration–time curve obtained by linear regression after semilogarithmic transformation. The area under the plasma concentration–time curve (AUC) from hour 0 to infinity ($AUC_{0\text{-}\infty}$) was calculated as follows: $AUC_{0\text{-}\infty} = AUC_{0\text{-}tx} + C_{tx}/\lambda_z$, where tx is the time of the last voriconazole concentration (C_{tx}) exceeding the limit of quantification. Partial AUC values with 0 and 10 hours ($AUC_{0\text{-}10}$) or 0 and 24 hours ($AUC_{0\text{-}24}$) as time limits were calculated by the linear trapezoidal rule. The apparent volume of distribution was calculated as follows: $V_z/F = D/(\lambda_z \cdot AUC_{0\text{-}\infty})$, where D is dose and F is oral bioavailability. The oral systemic clearance was calculated as follows: $CL/F = D/AUC_{0\text{-}\infty}$. The renal clearance during the time interval from 0 to 24 hours was calculated as follows: $CL_{renal\ 0\text{-}24} = Ae_{0\text{-}24}/AUC_{0\text{-}24}$, where $Ae_{0\text{-}24}$ is the amount of voriconazole excreted into urine during the time interval from 0 to 24 hours.

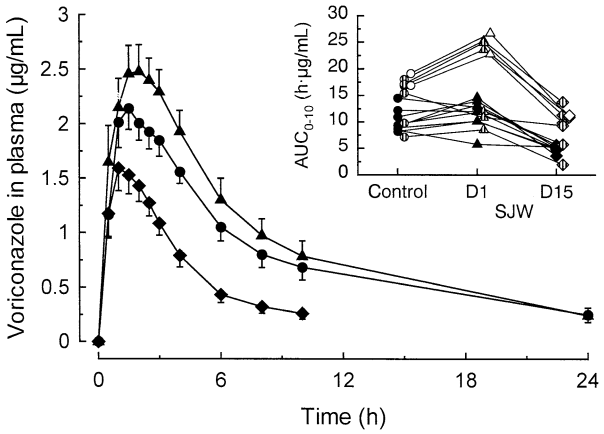

Fig 2. Mean (±SEM) plasma concentration–time curves of voriconazole before (*circles*) and on first day (D1 SJW, *triangles*) and last day (D15 SJW, *diamonds*) of daily coadministration of SJW (LI 160) for all participants (N = 16). *Inset*, Individual values for the area under the plasma concentration–time curve from 0 to 10 hours ($AUC_{0\text{-}10}$) during the 3 study parts shown for the CYP2C19 wild type (*solid symbols*) and genotypes **1/*2* (*hatched symbols*) and **2/*2* (*open symbols*).

Determination of CYP2C19 genotypes

The presence of the *CYP2C19*2* or **3* allele in the genomic deoxyribonucleic acid derived from leukocytes of the participants was determined by use of the hybridization probes format (LightCycler CYP2C19 Mutation Detection Kit with specific primers) on a LightCycler (both obtained from Roche Applied Science, Mannheim, Germany). The presence of the wild-type allele *CYP2C19*1* was inferred from the absence of the **2* and **3* alleles.

Statistical analysis

Data are expressed as mean values ± SD or mean values ± SEM (Fig 2). Differences in pharmacokinetic parameters of voriconazole between concomitant SJW treatment and control were assessed with the nonparametric Wilcoxon signed rank test for paired data. Differences in age, body weight, and body mass index and in the pharmacokinetic parameters of voriconazole between the *CYP2C19*1/*1* group and the combined *CYP2C19*1/*2* and **2/*2* group were assessed with the Wilcoxon rank sum (Mann-Whitney *U*) test for unpaired data. Assuming an SD of 30% for the difference in voriconazole AUC with and without SJW based on data for the interaction between SJW and omeprazole,[11] a sample size of 6 in each group was estimated to detect a 40% change in voriconazole AUC with a significance level of 5% and a statistical power of 90%. $P < .05$ was considered statistically significant.

RESULTS

Voriconazole was generally well tolerated by all participants, without serious adverse events. Transient enhanced light perception during the first hour after voriconazole intake was reported by most participants. This visual disturbance has been recognized as the most frequent adverse reaction to voriconazole and is related to transient electric changes in the retina but without detection of ocular lesions.[23] One participant (*CYP2C19*1/*1* genotype) discontinued the study after the first part because of elevated liver enzyme values and sonographic signs of hepatic steatosis possibly related to previous alcohol consumption.

The plasma concentration–time curves of voriconazole before and during SJW (LI 160) administration are shown in Fig 2. On the first day of SJW intake (D1 SJW), the $AUC_{0\text{-}10}$ of voriconazole was increased by 22% compared with control, whereas after 15 days of SJW administration (D15 SJW), the $AUC_{0\text{-}10}$ of voriconazole was reduced by 43% compared with control (Table I). $AUC_{0\text{-}10}$ values were taken for primary comparison because on D15 SJW, plasma concentrations of voriconazole were below the limit of quantification 24 hours after drug administration in 11 of 16 participants. The changes in C_{max} of voriconazole were similar to those in the $AUC_{0\text{-}10}$. In contrast, $AUC_{0\text{-}\infty}$ was not significantly changed on D1 SJW but was extensively reduced by 59% on D15 SJW. Correspondingly, CL/F of voriconazole was not affected on D1 SJW but was increased by 144% on D15 SJW. $AUC_{0\text{-}\infty}$ and CL/F varied widely between the participants (Fig 3). Despite an unchanged CL/F, the $t_{½}$ of voriconazole was already reduced on D1 SJW, with further reduction on D15 SJW. $CL_{renal\ 0\text{-}24}$ of voriconazole was only small compared with CL/F but yielded a significant reduction on D1 SJW (Table I).

When analyzed according to the different *CYP2C19* genotypes, $AUC_{0\text{-}10}$ and $AUC_{0\text{-}\infty}$ of voriconazole were not significantly changed on D1 SJW but were extensively reduced on D15 SJW in both the *CYP2C19* wild-type group and the *CYP2C19*1/*2* group (Table II). A similar trend occurred in the 2 participants with the *CYP2C19*2/*2* genotype. Corresponding results were obtained for CL/F in the 3 genetic groups (Fig 4). In the control phase, the CL/F of voriconazole was higher in the *CYP2C19* wild-type group than in the combined *CYP2C19*1/*2* and **2/*2* group (493 ± 123 mL/min versus 287 ± 199 mL/min, $P = .03$). On D15 SJW, the absolute increase in the CL/F of voriconazole

Table I. Pharmacokinetic parameters of single oral dose of 400 mg voriconazole before (control) and on first day and last day of coadministration of 300 mg St John's wort (LI 160) 3 times daily for all participants (N = 16)

Parameter	*Control*	*D1 SJW*	*P value**	*D15 SJW*	*P value**
$AUC_{0\text{-}10}$ (h · μg/mL)	12.7 ± 4.16	15.5 ± 6.84	.02	7.26 ± 3.43	.0004
$AUC_{0\text{-}\infty}$ (h · μg/mL)	23.5 ± 15.6	25.2 ± 16.2	.12	9.63 ± 6.03	.0004
C_{max} (μg/mL)	2.56 ± 0.56	3.13 ± 0.91	.02	1.87 ± 0.75	.001
t_{max} (h)	1.84 ± 0.94	1.75 ± 0.91	.97	1.25 ± 0.63	.01
$t_{½}$ (h)	8.18 ± 4.73	6.37 ± 2.45	.004	4.95 ± 1.34	.0005
V_z/F (L)	227 ± 80.5	180 ± 79.5	.03	377 ± 199	.0004
CL/F (mL/min)	390 ± 192	371 ± 215	.18	952 ± 524	.0004
$CL_{renal\ 0\text{-}24}$ (mL/min)	1.60 ± 0.92	1.31 ± 0.64	.04	2.20 ± 1.31†	.11†

Data are presented as mean ± SD.

D1 SJW, First day of St John's wort administration; D15 SJW, last day of St John's wort administration; $AUC_{0\text{-}10}$, area under plasma concentration–time curve from 0 to 10 hours; $AUC_{0\text{-}\infty}$, area under plasma concentration–time curve from hour 0 to infinity; C_{max}, peak plasma concentration; t_{max}, time to peak plasma concentration; $t_{½}$, terminal plasma elimination half-life; V_z/F, apparent volume of distribution; CL/F, oral systemic clearance; $CL_{renal\ 0\text{-}24}$, renal clearance during time interval from 0 to 24 hours.

**P* values are given for the differences with respect to control.

†Values were calculated for 15 participants because of a urine collection error in 1 participant.

compared with control was also higher in the *CYP2C19* wild-type group than in the combined *CYP2C19*1/*2* and **2/*2* group (675 ± 232 mL/min versus 448 ± 479 mL/min, $P = .02$), but the relative increase in the CL/F of voriconazole in relation to the control phase was not different between the *CYP2C19* wild-type group and the combined *CYP2C19*1/*2* and **2/*2* group (148% ± 66.8% versus 150% ± 67.3%, $P = .67$). Corresponding results were obtained for the $AUC_{0\text{-}\infty}$ of voriconazole in the control phase (14.3 ± 3.48 h · μg/mL versus 32.7 ± 17.7 h · μg/mL, $P = .03$) and the relative reduction in the $AUC_{0\text{-}\infty}$ on D15 SJW in relation to control (−57.1% ± 11.5% versus −57.9% ± 9.1%, $P = .67$) when the 2 genetic groups were compared.

DISCUSSION

The SJW preparation LI 160 has been used in most clinical studies investigating drug interactions with SJW. As a hyperforin-rich methanolic extract of SJW,[16] LI 160 induces intestinal and hepatic CYP3A4 and intestinal P-glycoprotein.[14] Consequently, the plasma AUC of orally administered substrates of CYP3A4 or P-glycoprotein is reduced by a mean range of 20% to 60%.[4,6,8,9,13,14] Because voriconazole is metabolized mainly by CYP2C19 and CYP3A4,[25] an interaction with SJW was expected. Knowing the extent of this interaction is essential, given the high prevalence of SJW exposure in hospitalized patients.[30]

In this study the reduction of the voriconazole $AUC_{0\text{-}\infty}$ by 59% after 15 days of LI 160 coadministration is similar to the AUC reduction of oral cyclosporine[18] and tacrolimus[8] and about twice as high as the AUC reduction of digoxin[4] after 2 weeks of daily treatment with 600 mg[8,18] and 900 mg LI 160,[4] respectively. The $t_{½}$ of digoxin remained unchanged after SJW treatment. Because digoxin is hardly metabolized but is a substrate of P-glycoprotein, the unchanged $t_{½}$ reflects a predominant influence on the intestinal absorption of digoxin limited by P-glycoprotein.[4] In this study the concomitant reduction of voriconazole's C_{max} (27%) and $t_{½}$ (39%) after 15 days of SJW intake suggests that both presystemic processes (intestinal absorption or intestinal first-pass metabolism) and systemic elimination of voriconazole are altered by prolonged intake of SJW. In previous studies on the interaction between SJW and the CYP3A4 substrate midazolam, the increase in the CL/F of midazolam was more than 3 times higher after oral administration than after intravenous administration, indicating that induction of intestinal CYP3A4 mainly contributes to the interaction.[7,31] Intestinal transport of voriconazole had not been described yet, but the related azole antifungal intraconazole was identified to be transported by P-glycoprotein.[32] Thus induction of both absorption-limiting drug transport proteins and intestinal metabolism might contribute to the reduction in voriconazole exposure after prolonged administration of SJW.

Rifampin (INN, rifampicin) is a well-known and potent inducer of CYP-mediated drug metabolism and P-glycoprotein–mediated drug transport. Most drugs interacting with rifampin are also known to interact with SJW in a similar way.[33] For drugs such as tacrolimus,[9] verapamil,[12] imatinib,[13] and digoxin,[14] the extent of reduction in exposure was higher after rifampin than after SJW administration. Coadministration of rifampin led to a 96% reduction in the AUC of voriconazole (German product labeling for voriconazole, Pfizer, Ger-

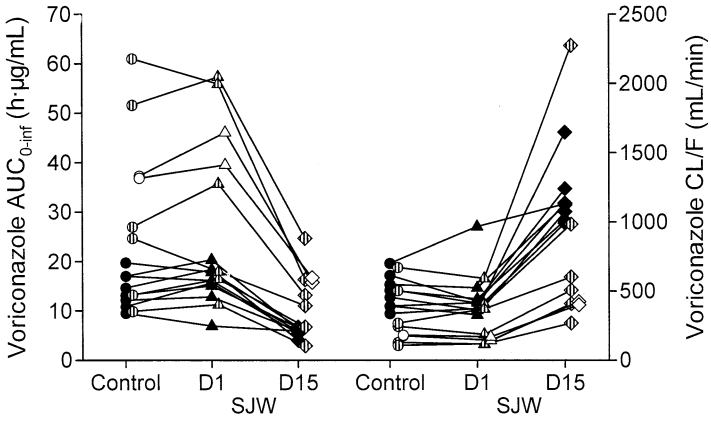

Fig 3. Individual values for area under plasma concentration–time curve from hour 0 to infinity ($AUC_{0\text{-}\infty}$) and oral systemic clearance (CL/F) of voriconazole before (*circles*) and on first day (D1 SJW, *triangles*) and last day (D15 SJW, *diamonds*) of daily coadministration of SJW (LI 160) shown for CYP2C19 wild type (*solid symbols*) and genotypes **1/*2* (*hatched symbols*) and **2/*2* (*open symbols*).

Table II. Mean exposure of voriconazole after single oral dose of 400 mg before and on first day and last day of coadministration of 300 mg St John's wort (LI 160) 3 times daily differentiated for CYP2C19 genotypes

Parameter	*Control*	*D1 SJW*	*P value**	*D15 SJW*	*P value**
CYP2C19 wild type (n = 8)					
$AUC_{0\text{-}10}$ (h · µg/mL)	10.2 ± 2.19	11.6 ± 2.85	.21	5.08 ± 0.65	.01
$AUC_{0\text{-}\infty}$ (h · µg/mL)	14.3 ± 3.48	15.4 ± 4.12	.26	5.84 ± 0.84	.01
*CYP2C19*1/*2* (n = 6)					
$AUC_{0\text{-}10}$ (h · µg/mL)	14.3 ± 4.49	17.7 ± 7.87	.12	8.84 ± 4.21	.03
$AUC_{0\text{-}\infty}$ (h · µg/mL)	31.2 ± 20.7	32.4 ± 20.5	.60	12.5 ± 7.61	.03
*CYP2C19*2/*2* (n = 2)					
$AUC_{0\text{-}10}$ (h · µg/mL)	18.1	24.8		11.2	
$AUC_{0\text{-}\infty}$ (h · µg/mL)	37.1	42.8		16.2	

Data are presented as mean ± SD.
**P* values are given for the differences with respect to control.

many, August 2004), which is also higher than the 59% reduction observed in our study. Apart from dose and factors related to tissue distribution, an inhibitory effect of SJW on CYP3A4 as observed in vitro[21,22] was suggested as a possible explanation for this difference.[12]

The effect of short-term coadministration of SJW on the pharmacokinetics of digoxin, caffeine, tolbutamide, dextromethorphan, and midazolam was investigated in 2 previous studies, without detection of significant changes.[4,31] In a further study a single dose of SJW led to a 45% increase in the C_{max} of fexofenadine, which is a substrate of P-glycoprotein.[34] In our study a 22% increase in the $AUC_{0\text{-}10}$ of voriconazole occurred on the first day of SJW administration. This increase was reflected also in C_{max} but not in $AUC_{0\text{-}\infty}$ or CL/F. These results suggest that the short-term effect of SJW is limited to the absorption phase of voriconazole. Several mechanisms for this effect can be discussed. First, acceleration of the dissolution of voriconazole tablets by constituents of SJW appears unlikely because the t_{max} of voriconazole remains unchanged. Second, apical intestinal export pumps such as P-glycoprotein might be inhibited either by hyperforin[34,35] or by the pharmaceutic aid Macrogol 6000, similar to P-glycoprotein inhibition by Cremophor RH40.[36] This inhibition might lead to enhanced absorption of voriconazole during the intestinal presence of the SJW preparation. Third, enhanced absorption of voriconazole might be related to a short-term inhibition of the intestinal voriconazole metabolism. The 50% inhibitory concentration (IC_{50}) values required for inhibition of CYP3A4 by hyperforin in vitro (2-4 µmol/L)[21,22] are much higher than the 50% effective concentration

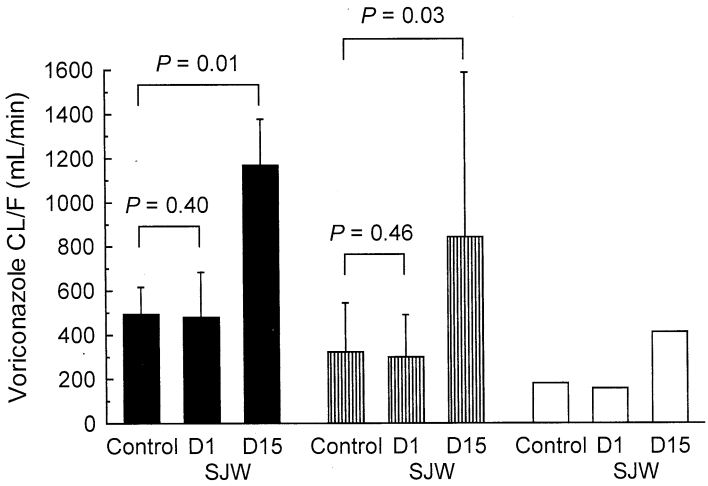

Fig 4. Mean (±SD) values for CL/F of voriconazole before (control) and on first day (D1 SJW) and last day (D15 SJW) of daily coadministration of SJW (LI 160) shown for CYP2C19 wild type (*solid bars*, n = 8) and genotypes **1/*2* (*hatched bars*, n = 6) and **2/*2* (*open bars*, n = 2).

(EC_{50}) value for PXR activation (23 nmol/L).[20] This supports the hypothesis that relevant inhibition can only be achieved locally in the gut whereas the lower systemic concentrations are sufficient for PXR activation and subsequent induction of metabolism and transport.

The basis for the reduction in the voriconazole $t_{½}$ after short-term administration of SJW remains unclear. First, oral voriconazole pharmacokinetics does not appear to have flip-flop characteristics because $t_{½}$ after oral intake is rather shorter than after intravenous administration.[37] Thus an unmasking of the "real" oral $t_{½}$ by SJW is unlikely. Second, a short-term increase in systemic voriconazole clearance by induction of metabolism is also unlikely because cell cultures were exposed to hyperforin for 48 hours to yield significant CYP induction.[19] Finally, an alteration of voriconazole metabolism by the preceding administration of voriconazole on study day 1 appears unlikely because autoinduction of voriconazole metabolism was only found in rats and dogs but was not observed in humans.[38] Third, the 20% reduction in the V_z/F of voriconazole on the first day of SJW administration observed in our study may be caused by an increase in oral bioavailability or by a reduction in the distribution of voriconazole. However, the absolute bioavailability of voriconazole is about 90%,[37,38] indicating that the observed change cannot be explained by a change in oral bioavailability alone. Thus a short-term reduction of the systemic voriconazole distribution by SJW, for example, by alteration of transport processes, may lead to the observed reduction in $t_{½}$ on the first day of SJW administration.

Voriconazole is metabolized mainly by CYP2C19 and CYP3A4.[25] Therefore genetic polymorphisms of *CYP2C19* are expected to influence the interaction with SJW. In the exploratory analysis of our study, the pattern of interaction was similar in the 3 genetic groups (*CYP2C19* wild type, *CYP2C19*1/*2*, and *CYP2C19*2/*2*) with a trend toward an increase in the $AUC_{0\text{-}10}$ of voriconazole on the first day of SJW intake and an extensive reduction in the $AUC_{0\text{-}\infty}$ after prolonged SJW intake. Because genetic screening included only the alleles **2* and **3*, which account for more than 85% of defective *CYP2C19* alleles in white subjects,[27] the occurrence of other defective alleles in the study population and thus misclassification of individuals cannot be ruled out.

For statistical comparison, data from individuals with *CYP2C19*1/*2* and **2/*2* genotype were pooled. In line with a previous report,[26] the presence of the deficient *CYP2C19*2* allele resulted in a higher baseline $AUC_{0\text{-}\infty}$ and lower CL/F of voriconazole compared with the *CYP2C19* wild-type group in our study. In addition, the absolute increase in the CL/F after prolonged intake of SJW was smaller in the presence of the *CYP2C19*2* allele compared with the wild-type group. Therefore the induction of voriconazole metabolism might not be limited to the induction of CYP3A4, which would be expected to result in equal absolute increases in CL/F in the 2 genetic groups. In addition, CYP2C19 also appears to be induced, leading to a smaller increase in CL/F in the presence of the *CYP2C19*2* allele (Fig 4). This hypothesis is supported by recent data on the induction of CYP2C19-mediated

metabolism of mephenytoin by SJW, where an increase in CYP2C19 activity occurred in the extensive metabolizer group but not in the poor metabolizer group.[28] PXR was found to up-regulate the transcription of CYP2C19[39]; thus it is reasonable that SJW might induce the metabolism of voriconazole, depending on both CYP3A4 and CYP2C19. Because the recommended voriconazole dosage is independent of the *CYP2C19* genotype (German product labeling for voriconazole, Pfizer, Germany, August 2004), combination therapy with potent inducers such as SJW might result in the lowest antifungal exposure in *CYP2C19* wild-type patients because of the highest CL/F of voriconazole achieved in this group.

In conclusion, coadministration of the SJW preparation LI 160 results in a short-term small and clinically irrelevant increase in voriconazole exposure, which is followed by an extensive reduction after prolonged administration of SJW. This halving of voriconazole exposure is probably of clinical relevance because plasma concentrations of voriconazole might fall below the levels needed for antifungal activity, although a clear correlation between plasma concentrations and efficacy of voriconazole was not yet been described.[40] In contrast to SJW, voriconazole is mainly used in the inpatient setting, but the recent finding of a prevalence of about 7% undeclared exposure to SJW in hospitalized patients[30] underlines the importance of considering this interaction in the clinical setting.

We thank Mrs Brigitte Tubach for study support and Mrs Andrea Deschlmayr, Mrs Magdalena Longo, and Mrs Jutta Kocher for their excellent technical assistance.

The Department of Internal Medicine VI, Clinical Pharmacology and Pharmacoepidemiology has received a grant from Pfizer, Germany, to establish and make available an HPLC method for the determination of voriconazole in plasma, which has been validated according to Food and Drug Administration standards. None of the authors has financial or personal relationships that could potentially be perceived as influencing the research described herein.

References

1. De Smet PAGM. Herbal remedies. N Engl J Med 2002; 347:2046-56.
2. Ruschitzka F, Meier P, Turina M, Lüscher T, Noll G. Acute heart transplant rejection due to Saint John's wort. Lancet 2000;355:548-9.
3. Schwarz U, Büschel B, Kirch W. Unwanted pregnancy on self medication with St John's wort despite hormonal contraception. Br J Clin Pharmacol 2003;55:112-3.
4. Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic and drug disposition: pharmacokinetic interaction of digoxin with a herbal extract from St John's wort (*Hypericum perforatum*). Clin Pharmacol Ther 1999;66:338-45.
5. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. Lancet 2000;355:547-8.
6. Bauer S, Störmer E, Johne A, Krüger H, Budde K, Neumayer H-H, et al. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. Br J Clin Pharmacol 2003;55:203-11.
7. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. Clin Pharmacol Ther 2003;73:41-50.
8. Mai I, Störmer E, Bauer S, Krüger H, Budde K, Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. Nephrol Dial Transplant 2003;18: 819-22.
9. Hebert MF, Park JM, Chen Y-L, Akhtar S, Larson AM. Effects of St. John's wort (Hypericum perforatum) on tacrolimus pharmacokinetics in healthy volunteers. J Clin Pharmacol 2004;44:89-94.
10. Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2004;57:592-9.
11. Wang L-S, Zhou G, Zhu B, Wu J, Wang J-G, El-Aty AMA, et al. St John's wort induces both cytochrome P450 3A4-catalyzed sufoxidation and 2C19-dependent hydroxylation of omeprazole. Clin Pharmacol Ther 2004; 75:191-7.
12. Tannergren C, Engman H, Knutson L, Hedeland M, Bondesson U, Lennernäs H. St John's wort decreases the bioavailability of *R*- and *S*-verapamil though induction of the first-pass metabolism. Clin Pharmacol Ther 2004;75: 298-309.
13. Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, Egorin MJ. Effect of St John's wort on imatinib mesylate pharmacokinetics. Clin Pharmacol Ther 2004;76:323-9.
14. Dürr D, Stieger B, Kullak-Ublick GA, Rentsch KM, Steinert HC, Meier PJ, et al. St John's wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. Clin Pharmacol Ther 2000;68:598-604.
15. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. Br J Clin Pharmacol 2002; 54:349-56.
16. Wurglics M, Westerhoff K, Kaunzinger A, Wilke A, Baumeister A, Dressman J, et al. Comparison of German St. John's wort products according to hyperforin and total hypericin content. J Am Pharm Assoc 2001;41:560-6.
17. Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, Hehl E-M, et al. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. Clin Pharmacol Ther 2004;75:546-57.

18. Mai I, Bauer S, Perloff ES, Johne A, Uehleke B, Frank B, et al. Hyperforin content determines the magnitude of the St John's wort–cyclosporine drug interaction. Clin Pharmacol Ther 2004;76:330-40.
19. Komoroski BJ, Zhang S, Cai H, Hutzler M, Frye R, Tracy TS, et al. Induction and inhibition of cytochromes P450 by the St. John's wort constituent hyperforin in human hepatocyte cultures. Drug Metab Dispos 2004;32: 512-8.
20. Moore LB, Goodwin B, Jones SA, Wisely GB, Serabjit-Singh CJ, Willson TM, et al. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. Proc Natl Acad Sci U S A 2000;97: 7500-2.
21. Obach RS. Inhibition of human cytochrome P450 enzymes by constituents of St. John's wort, an herbal preparation used on the treatment of depression. J Pharmacol Exp Ther 2000;294:88-95.
22. Zou L, Harkey MR, Henderson GL. Effects of herbal components on cDNA-expressed cytochrome P450 enzyme catalytic activity. Life Sci 2002;71:1579-89.
23. Johnson LB, Kauffmann CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis 2003;36:630-7.
24. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann J-W, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-15.
25. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the *N*-oxidation of voriconazole. Drug Metab Dispos 2003;31:540-7.
26. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther 2004;75:586-8.
27. Desta Z, Zhao X, Shin J-G, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet 2002;41:913-58.
28. Wang L-S, Zhu B, El-Aty AMA, Zhou G, Li Z, Wu J, et al. The influence of St. John's wort on CYP2C19 activity with respect to genotype. J Clin Pharmacol 2004;44:577-81.
29. Pennick GJ, Clark M, Sutton DA, Rinaldi MG. Development and validation of a high-performance liquid chromatography assay for voriconazole. Antimicrob Agents Chemother 2003;47:2348-50.
30. Martin-Facklam M, Rieger K, Riedel K-D, Burhenne J, Walter-Sack I, Haefeli WE. Undeclared exposure to St. John's wort in hospitalized patients. Br J Clin Pharmacol 2004;58:437-41.
31. Wang Z, Gorski C, Hamman MA, Huang S-W, Lesko LJ, Hall SD. The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. Clin Pharmacol Ther 2001;70:317-26.
32. Miyama T, Takanaga H, Matsuo H, Yamano K, Yamamoto K, Iga T, et al. P-glycoprotein-mediated transport of itraconazole across the blood-brain barrier. Antimicrob Agents Chemother 1998;42:1738-44.
33. Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. Arch Intern Med 2002;162:985-92.
34. Wang Z, Hamman MA, Huang SM, Lesko LJ, Hall SD. Effect of St John's wort on the pharmacokinetics of fexofenadine. Clin Pharmacol Ther 2002;71:414-20.
35. Wang E, Barecki-Roach M, Johnson WW. Quantitative characterization of direct P-glycoprotein inhibition by St John's wort constituents hypericin and hyperforin. J Pharm Pharmacol 2004;56:123-8.
36. Tayrouz Y, Ding R, Burhenne J, Riedel KD, Weiss J, Hoppe-Tichy T, et al. Pharmacokinetic and pharmaceutic interaction between digoxin and Cremophor RH40. Clin Pharmacol Ther 2003;73:397-405.
37. Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regime. Antimicrob Agents Chemother 2002;46:2546-53.
38. Roffey SJ, Cole S, Comby P, Gibson D, Jezequel SG, Nedderman ANR, et al. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog, and human. Drug Metab Dispos 2003;31:731-41.
39. Chen Y, Ferguson SS, Negishi M, Goldstein JA. Identification of constitutive androstane receptor and glucocorticoid receptor binding sites in the *CYP2C19* promoter. Mol Pharmacol 2003;64:316-24.
40. Lutsar I, Hodges MR, Tomaszewski K, Troke PF, Wood ND. Safety of voriconazole and dose individualization. Clin Infect Dis 2003;36:1087-8.