Effects of *Schisandra sphenanthera* extract on the pharmacokinetics of tacrolimus in healthy volunteers

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What is already known about this subject

- *Schisandra sphenanthera* extract (SchE) and tacrolimus are often co-administered in treating renal and liver transplant recipients in China.
- We discovered occasionally that blood tacrolimus concentrations are markedly increased in some patients who receive tacrolimus and concomitant SchE.
- This is the first study to investigate the effects of SchE on the pharmacokinetics of tacrolimus.

What this study adds

- Following administration of SchE in healthy volunteers, the mean AUC, AUMC and $C_{\max}$ of tacrolimus substantially increases, whereas its CL/F and V/F decreases significantly.
- Blood tacrolimus concentrations need to be closely monitored and dose adjustments of tacrolimus have to be made accordingly in the presence of SchE.

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Aim

To assess the effect of *Schisandra sphenanthera* extract (SchE) on the pharmacokinetics of tacrolimus in healthy volunteers.

Methods

Twelve healthy male volunteers were orally treated with SchE, three capsules twice daily for 13 days. Pharmacokinetic investigations of oral tacrolimus administration at 2 mg were performed both before and at the end of the SchE treatment period. Whole blood tacrolimus concentrations were determined by enzyme-linked immunosorbent assay. Estimated pharmacokinetic parameters before and with SchE were calculated with noncompartmental techniques.

Results

Following administration of SchE, the average percentage increases of individual increases in AUC, AUMC and $C_{\max}$ of tacrolimus were 164.2% [95% confidence interval (CI) 70.1, 258.4], 133.1% (95% CI 49.5, 261.3) and 227.1% (95% CI 155.8, 298.4), respectively ($P < 0.01$ or 0.05). On average, there was a 36.8% (95% CI 13.4, 60.2) increase in tacrolimus $t_{\max}$ ($P < 0.01$). The average percentage decreases in CL/F and V/F were 49.0% (95% CI 31.1, 66.9) and 53.7% (95% CI 40.1, 67.4), respectively ($P < 0.01$).

Conclusions

SchE can increase the oral bioavailability of tacrolimus. The results of this study will add important information to the interaction area between drugs and herbal products.

Introduction

Schisandra sphenanthera has thousands of years' history of medical use in China. Its major chemical constituents include schizandrin, deoxyschizandrin, schisanhenol, schizandrol, sesquicarene, β -chamigrene, citral, stigmasterol and vitamins C and E.

Previously published work has shown that several constituents isolated from *S. sphenanthera* can interact with CYP3A and/or P-glycoprotein (P-gp) [1–4]. Schizandrin B was recently found to function as a P-gp inhibitor [1, 2]. Gomisins A isolated from *Schinensis* has been shown to reverse P-gp-mediated multidrug resistance (MDR) by uncompetitive inhibition of substrate–P-gp association and inducing P-gp conformational changes that impede substrate transport [3]. It has been reported that gomisins C is a mechanism-based inhibitor that not only competitively inhibits but irreversibly inactivates CYP3A4 [4].

Schisandra sphenanthera extract (SchE) contains 11.25 mg deoxyschizandrin per capsule. It is a prescribed drug rather than a herbal supplement, which has been widely used to treat viral and drug-induced hepatitis in China. Concomitant use of SchE with CYP3A and/or P-gp substrates may produce interactions based on the inhibitory effects of some constituents included in SchE on CYP3A and/or P-gp. Tacrolimus emerged as an alternative calcineurin inhibitor during the early 1990s [5]. It has been used in place of ciclosporin A in patients with a variety of solid organ and other transplants. Tacrolimus is a substrate for both CYP3A and P-gp [6, 7]. The interaction between tacrolimus and herbal medicines or synthetic drugs has been reported [8, 9].

SchE and tacrolimus are often co-administered when drug-induced hepatitis occurs in transplant recipients. In treating renal and liver transplanted recipients, we have discovered that blood tacrolimus concentrations are occasionally markedly increased in some patients who receive tacrolimus and concomitant SchE (data not shown). The purpose of this study was to investigate the effects of SchE on the pharmacokinetics (PK) of tacrolimus in healthy volunteers.

Materials and methods

Subjects

Twelve healthy male volunteers 23.5 ± 1.2 years of age, 168.8 ± 3.8 cm in height and weighing 62.9 ± 5.1 kg participated in the trials. Before entering the study, each subject underwent a routine physical examination and laboratory investigations. Laboratory indices included liver and renal function, blood and urine routine and blood glucose. Volunteers were considered to be healthy if physical examination, medical history and standard

biochemical blood and urine tests were normal. Smokers and those taking medication were excluded. Informed consent was obtained according to the Declaration of Helsinki. The study was approved by the ethics committee of Wuhan General Hospital.

Trial design and blood sampling

In the morning of day 1, each volunteer received a single oral dose of 2 mg tacrolimus (Fujisawa Ireland Limited, Ireland). Venous blood samples (2 ml) were taken from an indwelling venous catheter into tubes containing ethylenediamine tetraacetic acid at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post dose. After the last sampling, subjects received three capsules of SchE (Hezheng Pharmaceutical Company, Chengdu, China, each capsule containing 11.25 mg deoxyschizandrin) twice daily for 13 days. On day 15, subjects were given another single oral dose of 2 mg tacrolimus, followed by three SchE capsules. The sampling times were the same as on day 1. On day 16, venous blood samples were taken to determine liver and renal functions, blood and urine routines and blood glucose.

Diet

Volunteers fasted from midnight until receiving their morning dose of tacrolimus on day 1 and day 15. Alcohol, caffeine-containing foods and beverages were not allowed from 72 h before the study until the end of the trial. To control for the effects of food on tacrolimus PK [10, 11], all subjects received the same diet at the same time on both tacrolimus administration days.

Analysis of blood sample

Whole-blood tacrolimus concentrations were determined by the PRO-Trac™ II Tacrolimus ELISA assay (DiaSorin Inc., Stillwater, MN, USA) [12–14]. The assay was run on a microtitre 96-well plate after pre-coating with goat antimouse IgG. Standards, controls and blood samples were extracted with a proprietary reagent and then added to the wells of the microtitre plate, followed by addition of antitacrolimus monoclonal antibody. After a 20-min incubation at room temperature, tacrolimus–horseradish peroxidase conjugate was added and incubated for an additional 60 min. The wells were then washed and chromogen added for a 15-min incubation. This reaction was stopped by addition of sulphuric acid and the absorbance in each well was read at 450 nm. In addition to the blood samples, a six-point standard curve, a point of nonspecific binding and two internal controls (low and high values) were mandatory. The calibration curve range was 0.3–30 ng mL⁻¹. The

interassay % coefficient of variation was 9.3% at the target concentration of 8 ng mL⁻¹.

Pharmacokinetic calculations

The PK parameters included: area under the blood concentration–time curve (AUC), area under the moment curve (AUMC), elimination half life ($t_{1/2}$), maximum blood drug concentration ($C_{\max}$), time to $C_{\max}$ ($t_{\max}$), apparent oral volume of distribution (V/F), apparent oral clearance (CL/F). $C_{\max}$ and $t_{\max}$ were determined by visual inspection of the blood concentration–time curves. The other parameters such as $t_{1/2}$ were calculated using noncompartmental model with Pharmacokinetic Program DAS 2.0 (Chinese Pharmacological Society, Beijing, China). For the above parameters, a 95% confidence interval (CI) for the increased or decreased percentage of treatment before SchE to that after SchE was estimated. The 90% CI for the ratio of tacrolimus AUC after SchE to that before SchE was constructed. A drug–drug interaction was assumed if the 90% CI did not fall within the prespecified interval of 80–125%.

Statistical analysis

Statistical calculations were carried out using SPSS software v.10.0 (SPSS Inc., Chicago, IL, USA). AUC and $C_{\max}$ were log transformed prior to analysis with the paired Student's *t*-test. Wilcoxon's signed rank test was used to evaluate the differences on $t_{\max}$. All other parameters were assessed using the paired Student's *t*-test. $P < 0.05$ was considered to be statistically significant.

Results

The blood concentration–time curve of tacrolimus prior to and after the co-administration of SchE in 12 healthy volunteers is shown in Figure 1. Individual PK parameters of tacrolimus in whole blood are given in Table 1. Individual data on tacrolimus AUC before and after SchE are shown in Figure 2.

After coadministration of SchE, the average percentage increases of individual increases in AUC, AUMC and $C_{\max}$ of tacrolimus were 164.2% (95% CI 70.1, 258.4), 133.1% (95% CI 49.5, 261.3) and 227.1% (95% CI 155.8, 298.4), respectively ($P < 0.01$ or 0.05). The 90% CI for the ratio of tacrolimus AUC after SchE to that before SchE was 187.3–341.2%. On average, there was a 36.8% (95% CI 13.4, 60.2) increase in tacrolimus $t_{\max}$ ($P < 0.01$). The average percentage decreases in CL/F and V/F were 49.0% (95% CI 31.1, 66.9) and 53.7% (95% CI 40.1, 67.4), respectively ($P < 0.01$). No significant changes were seen in tacrolimus half life.

Measurements of hepatic and renal functions and other indices are shown in Table 2. These laboratory

Figure 1

Mean blood concentration–time curves of tacrolimus in 12 healthy volunteers. Before SchE (◆), with SchE (■)

Figure 2

Individual data for the effect of *Schisandra sphenantheral* extract (SchE) on tacrolimus AUC

indices included serum total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, total protein, globulin, albumin, urea nitrogen (BUN), creatinine (Cr), blood glucose, white blood cells, red blood cells, haemoglobin and platelets. Compared with before co-administration of SchE, the mean Cr level with SchE was lower and the mean BUN was higher in

Table 1

The tacrolimus pharmacokinetic parameters of 12 healthy volunteers before and after co-administration of SchE

Subject no.	AUC ₀₋₂₄ ($\mu\text{g l}^{-1} \text{h}^{-1}$)	AUMC ₀₋₂₄ ($\mu\text{g l}^{-1} \text{h}^{-1}$)	CL/F (l h^{-1})	V/F (C) (l)	$t_{1/2}$ (h)	t_{max} (h)	C_{max} ($\mu\text{g l}^{-1}$)
Before SchE							
1	125.3	895.6	15.8	93.6	4.1	1.5	23.3
2	55.7	518.4	30.1	451.2	10.4	1.5	13.3
3	83.8	458.9	23.5	148.8	4.4	1.5	19.8
4	257.3	1941.9	5.5	136.4	17.1	2	50.6
5	154.9	1184.0	10.7	163.4	10.6	1.5	21.5
6	81.9	425.4	24.3	110.0	3.1	2	16.3
7	107.9	1196.4	7.7	261.2	23.5	1	18.8
8	137.1	1011.4	11.9	191.4	11.1	1.5	23.3
9	232.2	1877.6	7.4	96.8	9.1	1	22.9
10	40.2	286.7	49.6	200.9	2.8	1	9.5
11	155.6	1277.8	11.4	147.4	9.0	1	31.7
12	122.1	1064.3	14.8	158.2	7.4	1.5	15.5
Mean	129.5	1011.5	17.7	179.9	9.4	1.4	22.2
SD	65.1	538.0	12.6	97.6	6.1	0.4	10.6
After SchE							
1	312.1	1958.8	5.5	73.9	9.3	2	65.3
2	194.3	1383.9	8.9	115.4	9.1	1.5	36.2
3	211.2	931.2	7.8	58.5	5.2	2	63.6
4	367.4	2159.3	5.1	54.3	7.3	2	74.9
5	350.8	2424.2	4.2	94.4	15.5	2	96.6
6	345.3	2326.6	4.8	77.8	11.2	1.5	88.3
7	284.1	1121.7	6.0	42.0	4.8	2	81.8
8	215.6	880.4	7.5	60.1	5.5	2	66.3
9	246.5	1030.2	7.5	29.8	2.8	2	53.4
10	257.6	2079.5	7.4	61.3	5.7	1.5	40.4
11	326.5	1825.2	5.3	82.1	10.7	1.5	92.7
12	186.6	1513.5	8.4	124.1	10.3	2	37.8
Mean	274.8**	1636.2*	6.5**	72.8**	8.1	1.8**	66.4**
SD	64.9	563.0	1.5	28.1	3.6	0.25	21.3

Compared with before coadministration with SchE: * $P < 0.05$; ** $P < 0.01$. SchE, Schisandra sphenanthera extract.

the presence of SchE ($P < 0.05$), but the values were still in the normal range. No significant changes were observed in the other indices. On day 15, about 1 h after coadministration of tacrolimus and SchE, six subjects complained of pyrosis and burning hands and feet. Their symptoms gradually disappeared within 10 h. No other adverse effects were observed.

Discussion

Studies have shown that pharmacokinetic parameters of tacrolimus vary greatly between healthy volunteers and patients [15, 16]. The variability in AUC and $t_{1/2}$ of tacrolimus was also observed between healthy volunteers in our present study. Tacrolimus is metabolized by CYP3A4 and CYP3A5 [6]. P-gp also plays an important role in the absorption metabolism of tacrolimus [17]. The

polymorphic nature of CYP3A-isoenzyme and *MDR1*, the gene coding P-gp, might contribute to the large individual variability in tacrolimus PK observed in the present study as well as in several other studies [18, 19].

Before treatment with SchE, the mean peak concentration of tacrolimus was at 1.4 h and $t_{1/2}$ was 9.4 h. These results are similar to those previously observed following single-dose oral administration of tacrolimus [15, 16]. After co-administration with SchE, the average increases in AUC of tacrolimus reached 164.2% and the mean C_{max} of tacrolimus increased to $66.4 \mu\text{g l}^{-1}$ from $22.2 \mu\text{g l}^{-1}$ in the absence of SchE. The side-effects, such as pyrosis, observed in six subjects may be explained by the marked increase in tacrolimus C_{max} in the presence of SchE. With the treatment of SchE, the t_{max} of tacrolimus significantly increased and CL/F decreased markedly.

Table 2

Liver function and renal function as well as other indices of 12 healthy volunteers before and after co-administration of SchE (mean $\pm$ SD)

Index	Before co-administration with SchE	After co-administration with SchE
TB ($\mu\text{mol l}^{-1}$)	12.26 $\pm$ 3.37	12.69 $\pm$ 5.15
DB ($\mu\text{mol l}^{-1}$)	3.20 $\pm$ 1.06	3.24 $\pm$ 1.84
ALT (U l^{-1})	13.20 $\pm$ 9.01	12.25 $\pm$ 5.93
AST (U l^{-1})	16.50 $\pm$ 3.00	17.25 $\pm$ 2.63
TP (g l^{-1})	74.16 $\pm$ 2.99	72.01 $\pm$ 3.15
G (g l^{-1})	28.68 $\pm$ 2.22	27.08 $\pm$ 2.88
A (g l^{-1})	45.48 $\pm$ 1.55	44.93 $\pm$ 1.83
BUN (mmol l^{-1})	4.46 $\pm$ 1.23	5.31 $\pm$ 1.46*
Cr ($\mu\text{mol l}^{-1}$)	76.34 $\pm$ 8.72	71.92 $\pm$ 7.35*
GLU (mmol l^{-1})	4.48 $\pm$ 0.47	4.37 $\pm$ 0.28
WBC ($\times 10^9 \text{ l}^{-1}$)	5.63 $\pm$ 1.07	5.38 $\pm$ 0.55
RBC ($\times 10^{12} \text{ l}^{-1}$)	4.89 $\pm$ 0.37	4.90 $\pm$ 0.23
Hb (g l^{-1})	146.80 $\pm$ 11.21	146.17 $\pm$ 6.85
Plt ($\times 10^9 \text{ l}^{-1}$)	173.80 $\pm$ 38.01	176.25 $\pm$ 34.80

Compared with before co-administration with SchE: * $P < 0.05$; ** $P < 0.01$. TB, Total bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; G, globulin; A, albumin; BUN, urea nitrogen; Cr, creatinine; GLU, blood glucose; WBC, white blood cells; RBC, red blood cells; Hb, haemoglobin; Plt, platelets.

The decrease in CL/F is probably a result of increased bioavailability of tacrolimus, as $t_{1/2}$ was not increased, but decreased.

Tacrolimus metabolism and transport are known to be induced or decreased by multiple drugs [8, 20]. St John's wort, also a herbal product, has been reported to decrease tacrolimus AUC significantly, as well as t_{max} and t_{min} in healthy volunteers and renal transplant recipients [9, 21]. The influence of St John's wort on tacrolimus PK may be attributed to induction of CYP3A4 and P-gp [22, 23]. Ketoconazole, a potent inhibitor of CYP3A4 and P-gp, has been observed to increase markedly the oral bioavailability of tacrolimus in healthy volunteers [8]. The increase in tacrolimus bioavailability could be explained by ketoconazole having a local inhibitory effect on tacrolimus gut metabolism or on intestinal P-gp activity [8].

Extrahepatic metabolism by CYP3A4 in the gastrointestinal epithelium is responsible for presystemic elimination of about half of the absorbed dose of tacrolimus [24]. The extent of absorption of tacrolimus from the gastrointestinal tract is also influenced by the activity of P-gp on enterocytes. SchE contains many substances, only a few of which have been investigated for their CYP3A- and P-gp-modulating activity. It has been demonstrated that schisandrin B and gomisin A are inhibitors of P-gp and gomisin C is an inhibitor of CYP3A4 [1–4].

Therefore, the observed increased AUC of tacrolimus induced by SchE could be due to inhibition of CYP3A4 and/or P-gp in the intestine, resulting in increased absorption and decreased gut metabolism. As regards the mechanism of the interaction, it would be of great value to determine the metabolites of tacrolimus as well as the parent drug. In addition, an intravenous administration study of tacrolimus would also help in the complete understanding of the mechanism involved.

The interaction between traditional Chinese medicine and immunosuppressants has been widely reported. Our previous work has shown that berberine could markedly elevate the blood concentration of ciclosporin A in healthy volunteers and renal transplant recipients in both clinical and PK studies [25, 26]. We have been working on the interaction between berberine and ciclosporin A so as to make use of berberine as a ciclosporin-sparing agent. To the best of our knowledge, this is the first study to investigate the interaction between tacrolimus and SchE. The results will add important information to the study of interaction between drugs and herbal products and also help in better use of tacrolimus in patients with SchE. Like berberine, SchE has slight side-effects and it is also cheap. With the great increase of tacrolimus bioavailability by SchE, a reduction in tacrolimus dosage may be possible and a consequent decrease in the therapeutic

tic cost of tacrolimus. Nevertheless, further investigation, especially on transplant recipients, is required.

Tacrolimus has a narrow therapeutic window and its whole blood trough concentrations should preferably be kept below 20 ng ml⁻¹ to avoid side-effects such as nephrotoxicity, neurotoxicity and infection [27, 28]. However, concentrations < 10 ng ml⁻¹ are associated with an increased risk of acute rejection [29]. Since the 90% CI for the AUC was much higher than the prespecified interval of 0.8–1.25, interaction between tacrolimus and SchE must be considered to be clinically significant. Thus, frequent monitoring of blood tacrolimus concentration is highly recommended when co-administration with SchE is unavoidable. Since both doctors and patients generally assume that SchE is safe, their education regarding this interaction is essential.

In conclusion, SchE treatment results in a substantial increase in the relative bioavailability of tacrolimus. If SchE is still the choice of hepato-protective drug, blood tacrolimus concentrations need to be closely monitored and dose adjustments made accordingly.

Competing interests: None declared.

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