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Full Length Research Paper

Pharmacokinetics of oral administration of 2, 3, 5, 4'-tetrahydroxystilbene-2-O-β-d-glucoside from *Polygonum multiflorum* in beagle dogs

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Pharmacokinetics studies of traditional Chinese medicine are increasingly showing its importance and necessity. In this study, we aim to determine the pharmacokinetics of oral administration of 2,3,5,4'-tetrahydroxystilbene-2-O-β-d-glucoside (SBGC) from *Polygonum multiflorum* or *P. multiflorum* extracting in Beagle dogs. Beagle dogs were fed with SBGC (2.0, 1.5 and 1.0 g/kg body weight) or *P. multiflorum* extracts (2.5 g/kg body weight) by oral gavage. We then examined pharmacokinetic parameters, including the area under the plasma concentration-time curve, maximum plasma concentration, time to maximum plasma concentration, half-life of absorption, half-life of distribution, half-life of elimination, and average drug retention time in the blood. The basic pharmacokinetic characteristics were similar between these two situations. When Beagle dogs were fed with *P. multiflorum* extracts, SBGC was absorbed and distributed faster, but the elimination speed remained at the same level. The current findings provide a clear guidance for the clinical application of *P. multiflorum*.

Key words: Pharmacokinetics, beagle dogs, *Polygonum multiflorum*, 2,3,5,4'-tetrahydroxystilbene-2-O-β-d-glucoside.

INTRODUCTION

The metabolism of traditional Chinese medicine in the body involves chemical changes in the structure of the compounds, known as biotransformation. Most of the pharmacological activities of Chinese medicine are lost during this metabolic process. Some traditional Chinese medicines can produce pharmacologically active or toxic metabolites during this process. Therefore, understanding the pharmacokinetics of metabolism of traditional Chinese medicine not only offers the knowledge of the strength and duration of the drugs, but also sheds light on the safety of these drugs. Therefore, pharmacokinetics studies of traditional Chinese medicine are increasingly showing its importance and necessity (Chai and Pan, 2006; Zeng et al., 2011).The dry roots of *Polygonum multiflorum* have been used as a traditional Chinese medicine for more than two thousand years. *P. multiflorum* can produce a variety of therapeutic functions, including detoxification, laxative for constipation, curing rubella itching, reducing carbuncle as well as high lipids (Chai and Pan, 2006). Stilbene glycosides (SBGC) is the main active ingredient of *P. multiflorum*, which can significantly improve immune function, produce anti-aging effect, lower blood pressure and cholesterol, and prevent atherosclerosis (Zeng et al., 2011; Lv et al., 2011; Xu et al., 2011; Wang et al., 2011; Li et al., 2010).

In this study, the pharmacokinetics of *P. multiflorum* and its main active ingredient SBGC were studied in canine models. The beagle dogs were fed with *P. multiflorum* extracts or SBGC at different doses and the pharmacokinetics dynamic characteristics were studied to

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provide the basis for its clinical application.

MATERIALS AND METHODS

Subjects

Healthy adult Beagle dogs weighing 10 ± 1 kg were purchased from Beijing Tongli experimental animal facility and housed in standard animal facility in the university. All experimental protocols were approved by the ethical committee of Beijing University of Chinese Medicine.

Reagents

P. multiflorum dry roots were purchased from Beijing Tongrentang Pharmacy; polydatin and SBGC were purchased from Chinese Medicine and Biological Products Co.; cleaner C18 SPE solid phase extraction column was purchased from Beijing Yijier Technology Co.; AB-8 macroporous resin was purchased from Nankai University Chemical Plant; and acetonitrile was purchased from Sigma-Aldrich.

Drug administration

P. multiflorum extracts and SBGC were prepared as previously reported (Lv et al., 2011). According to the guideline of pharmacokinetics research, the limit of quantitation (LOQ) is defined as the ability to detect plasma concentration after three to five elimination half-life cycles or at 1/10 to 1/20 maximum plasma concentration (C_{max}). Based on the sensitivity of various detection methods, the pilot test determined the high, medium, and low-dose of SBGC at 2.0, 1.5, 1.0 g/kg body weight, respectively.

Beagle dogs were fasted for 18 h before treatment. On the day of experiment, they were randomly divided into three treatment groups (n = 3 per group), receiving high, medium, and low doses of SBGC by oral gavage (corresponding SBGC doses were 1.04, 0.78, 0.52 g/kg body weight) or a single dose of *P. multiflorum* extracts by oral gavage (2.5 g/kg body weight). 5 ml of hind limb vein blood was collected 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, and 360 min after drug treatment. Blood samples were treated with heparin and centrifuged at 3000 r/min for 10 min. The upper part (plasma) was collected and stored at -40°C for later use.

Determination of plasma concentration

The samples were analyzed daily as a batch, including the standard curve samples, quality control (QC) samples, and test samples. Test results of QC samples were used to determine the effectiveness of measurement. The requirement was that for each batch of six QC samples, at least four of them had relative error within ± 15%; for two different concentrations of QC, the relative error was also within ± 15%. The plasma concentrations of SBGC were determined using Waters 1525 high-performance liquid chromatography.

Data processing

The DAS software was used to fit the SBGC plasma concentration-time curve. The F test and AIC values were used to determine the compartment model for SBGC pharmacokinetic parameters. Regarding the compartment model, for the same weight value, when F test was significant ($p < 0.05$), the model was based on a compartment value where AIC value was smaller; when F test was not significant ($p > 0.05$), and the model was based on a smaller compartment value. Regarding the choice of weight, the value of goodness of fit was compared to obtain the smaller number. If the values were similar, the value was based on LOQ, maximum absolute error, and relative error.

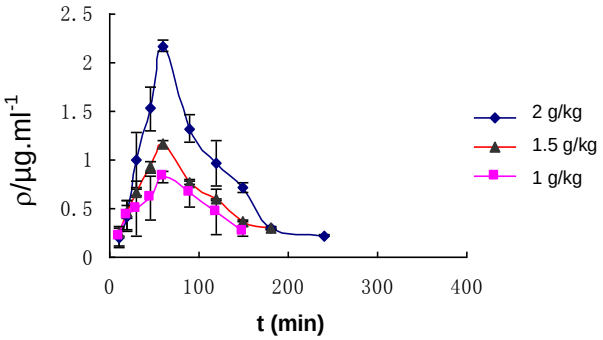

Figure 1. The time curve of SBGC plasma concentration after SBGC administration.

RESULTS AND DISCUSSION

The time curve of SBGC plasma concentration after three different doses (2.0, 1.5 and 1.0 g/kg body weight) of SBGC administration was shown in Figure 1.

The SBGC plasma concentrations were fitted using the DAS software. The time curves of high-, middle-, and low-dose groups were all in line with non-intravenous two-compartment model. The best fitting of the pharmacokinetic parameters for this model was: two-compartment model with the weight of $1/C^2$. The detailed pharmacokinetic parameters were summarized in Table 1.

The time curve of SBGC plasma concentration after the *P. multiflorum* extracts administration (2 g/kg body weight) is shown in Figure 2.

The SBGC plasma concentrations were fitted using the DAS software. The time curve of drug administration was in line with non-intravenous two-compartment model. The best fitting of the pharmacokinetic parameters for this model was: Two-compartment model with the weight of $1/C^2$. The detailed pharmacokinetic parameters were summarized in Table 2.

Pharmacokinetic studies provide important information on drug kinetics, exposure, metabolism, and dose schedule. We conducted a pharmacokinetic study on SBGC from *P. multiflorum*.

Beagle dogs were fed with SBGC (2.0, 1.5, and 1.0 g/kg body weight) by oral gavage and the pharmacokinetic results are in line with a two-compartment open model which is different from what has been reported on oral gavage in rats (Sun et al., 2005). SBGC is quickly absorbed in the intestine and can be detected in the blood 10 min after administration. The plasma concentration of SBGC peaks 1 h after oral gavage and reaches its trough level at 6 h.

Table 1. Pharmacokinetic parameters of plasma SBGC after SBGC administration.

Parameter	Dose (g/kg body weight)		
	1	1.5	2
C_{max}/mg·L^{-1}	0.83 ± 0.04	1.16 ± 0.06	2.17±0.23
t_{max}/h	1.00	1.00	1.00
$t_{1/2\alpha}$/h	0.20 ± 0.02	0.10 ± 0.02	0.14±0.02
$t_{1/2\beta}$/h	0.56 ± 0.05	0.60 ± 0.03	0.64±0.15
$t_{1/2k\alpha}$/h	0.39 ± 0.03	0.42 ± 0.05	0.26±0.06
AUC_{0-6}(mg·h·L^{-1})	1.53 ± 0.07	2.37 ± 0.06	3.68±0.02
$AUC_{0-\infty}$(mg·h·L^{-1})	2.04 ± 0.02	3.50 ± 0.19	4.59±0.35
V_L/L·kg^{-1}	0.08 ± 0.03	0.15 ± 0.05	0.08±0.04
$CL_{(s)}$/L·h^{-1}	0.11 ± 0.05	0.20 ± 0.07	0.16±0.06

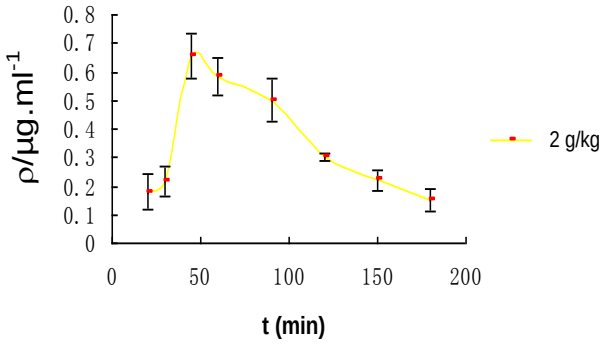

Figure 2. The time curve of SBGC plasma concentration after *P. multiflorum* extracts administration.

Table 2. Pharmacokinetic parameters of plasma SBGC after *P. multiflorum* extract administration.

Parameters	Dose (g/kg body weight)
	2
C_{max}/mg·L^{-1}	0.66 ± 0.06
t_{max}/h	1.00
$T_{1/2\alpha}$/h	0.06 ± 0.00
$T_{1/2\beta}$/h	0.79 ± 0.33
$T_{1/2k\alpha}$/h	0.24 ± 0.09
AUC_{0-6} (mg·h·L^{-1})	1.02 ± 0.07
$AUC_{0-\infty}$ (mg·h·L^{-1})	1.71 ± 0.25
V_L/L·kg^{-1}	0.01 ± 0.00
$CL_{(s)}$/L·h^{-1}	0.12 ± 0.02

The area under the plasma concentration-time curve (AUC) is proportional to the medication dosage and thus serves as an important parameter to evaluate drug bioavailability. After oral gavage of 2.0, 1.5, 1.0 g/kg SBGC, $AUC_{0-\infty}$ (mg•h•L^{-1}) is 4.59 ± 0.35, 3.50 ± 0.19, and 2.04 ± 0.02, respectively, and is positively associated with dosage.

t_{max} is the time to maximum plasma concentration. $t_{1/2}$ka is the half-life of absorption. Both values reflect the speed of drug absorption, with smaller values indicating faster absorption. After oral gavage of 2.0, 1.5, 1.0 g/kg SBGC, t_{max} is 1 h, and $t_{1/2}$kα is 0.26 ± 0.06, 0.42 ± 0.05, and 0.39 ± 0.03 h, respectively. Both values are relatively small, suggesting that SBGC can be quickly absorbed in the body.

C_{max} is the maximum plasma concentration after oral administration of drugs and is commonly used to indicate whether the plasma drug concentration reaches effective or toxic dosages. C_{max} can also reflect the intensity of the pharmacological action of drugs. After oral gavage of 2.0, 1.5, 1.0 g/kg SBGC, C_{max} is 2.17 ± 0.23, 1.16 ± 0.06 and 0.83 ± 0.04 mg/L, respectively, suggesting that C_{max} increases with dosage and the plasma SBGC concentration does not reach the toxic level.

$t_{1/2}$α is the half-life of distribution. $t_{1/2}$β is the half-life of elimination. $CL_{(s)}$ is the average drug retention time in the blood. These three values reflect the speed of drug elimination in the body. After oral gavage of 2.0, 1.5, 1.0 g/kg SBGC, $t_{1/2}$α is 0.14 ± 0.02, 0.10 ± 0.02, and 0.20 ± 0.02 h, respectively; $t_{1/2}$β is 0.64 ± 0.15, 0.60 ± 0.03, and 0.56 ± 0.05 h, respectively; and $CL_{(s)}$ is 0.16 ± 0.06, 0.20 ± 0.07, and 0.11 ± 0.05 L/h, respectively. These values suggest that SBGC is quickly distributed and eliminated and thus has a relatively short average retention time in the body.

We further fed Beagle dogs with *P. multiflorum* extracts (2.5 g/kg body weight) by oral gavage and then examined the pharmacokinetics. The pharmacokinetic results are in line with a two-compartment open model. SBGC from the *P. multiflorum* extracts is quickly absorbed in the intestine and can be detected in the blood 20 min after administration. The plasma concentration of *P. multiflorum* extracts peaks 0.75 h after oral gavage and reaches its trough level at 3 h, suggesting that *P. multiflorum* extracts are absorbed and eliminated faster than SBGC. When fed with *P. multiflorum* extracts by oral gavage, the corresponding SBGC concentration is 0.36 g/kg, much lower than when fed with SBGC by oral gavage (1.04, 0.78, and 0.52 g/kg). Therefore, we only measured plasma concentration at 20, 30, 45, 60, 90, 120, 150 and 180 min. After fed with *P. multiflorum* extracts, 2.5 g/kg, $AUC_{0-\infty}$ is 1.71 ± 0.25 mg•h•L^{-1}, which, similar with the case of SBGC, is positively associated with the dosage. t_{max} is 0.75; $t_{1/2}$ka is 0.24 ± 0.09 h; $t_{1/2}$α is 0.04 ± 0.00 h; and $t_{1/2}$β is 0.79 ± 0.33 h. All these values indicate that when Beagle dogs are fed with *P. multiflorum* extracts, SBGC is absorbed and distributed fast. Elimination speed remains the same. The basic pharmacokinetic parameters are similar between these two situations.

It is a promising strategy to substitute traditional Chinese medicine with a single herb that can achieve the same treatment efficacy. Recently, studies have used the pharmacokinetic-pharmacodynamic (PK-PD) model to

examine the pharmacokinetics of traditional Chinese medicine, focusing on the relationship among drug plasma concentration, pharmacological effects, and toxicity. Wang and Huang (1992) examined the pharmacokinetics of matrine and oxymatrine using the PK-PD model and found that although the efficacy is not directly related to the plasma concentration, the efficacy and effect-site concentration are in line with the E_{max} model. Zhou et al. (1996, 1999) studied the pharmacokinetics of sinomenine and Dinggong vine and revealed that drug plasma concentration is related to toxicity within a certain time frame. Li et al. (1999) proposed that drug-containing plasma can be used directly in pharmacokinetic studies in order to eliminate confounding effects, including animal species, physical, and environmental factors.

Conclusion

The PK-PD model combines drug concentration, efficacy, and duration and provides a dynamic picture of how drugs behave in the body. This model can be employed in future studies to reveal underlying mechanisms and indentify effective components of the traditional Chinese medicine.

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