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Effect of Curcumin on Sulfasalazine Pharmacokinetics in Healthy Volunteers

Tomoko Tokumoto[1], Takeshi Hirota[1], Keisuke Gotanda[1], Miyuki Kimura[2], Shin Irie[2], Masato Fukae[1] and Ichiro Ieiri[1*]

[1]*Department of Clinical Pharmacokinetics, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan*

[2]*Clinical Research Unit, Sugioka Memorial Hospital, Fukuoka, Japan*

[*]**Corresponding author:** Ichiro Ieiri, Department of Clinical Pharmacokinetics, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan, Tel: +81 92 642 6656; Fax: +81 92 642 6660; E-mail: ieiri-ttr@umin.ac.jp

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Abstract

Curcumin, a commonly used spice, is a naturally occurring polyphenol. It has been reported that curcumin inhibited the transport activity of breast cancer resistance protein (BCRP/ABCG2) in animal studies, and curcumin caused significantly increased plasma concentrations of sulfasalazine (SASP), an *in vivo* probe for BCRP function in human. In this study, we assessed the influence of prior administration of curcumin on the pharmacokinetics of SASP. An open-label, single-arm and two-phase study was conducted in 34 healthy participants. A single dose of SASP (2,000 mg) was administered orally after overnight fast (phase 1). After seven days washout period, a single oral dose of curcumin (2,000 mg) was administered, and then, 4 days to 5 days after administration of curcumin, 2,000 mg of SASP was administered orally again (phase 2). Plasma concentrations of SASP were assayed by high-performance liquid chromatography. Orally 4 days to 5 days' time lag between SASP and curcumin intake disappeared the interaction. The disappeared interaction may be responsible for the extremely low bioavailability of curcumin and the disappearance of curcumin in the gastro-intestinal tracts before the administration of SASP. Our findings suggested that 4 days to 5 days' time lag is necessary to avoid the drug interaction between BCRP substrates and curcumin.

Keywords: Breast cancer resistance protein; ABCG2; Curcumin; Sulfasalazine; Pharmacokinetics

Abbreviations

BCRP/ABCG2: Breast Cancer Resistance Protein; SASP: Sulfasalazine; ANOVA: Analysis of Variance

Introduction

Curcumin, a major component of turmeric, has a wide spectrum of biological and pharmacological effects including anti-inflammatory, anti-oxidant, and anti-angiogenic activities [1]. Transcriptional factors, growth factors, inflammatory cytokines, protein kinases and other enzymes have been identified as targets of curcumin. The pharmacokinetic-related genes have also been identified as targets of curcumin [2]. Breast cancer resistance protein (BCRP/ABCG2), a half-molecule ATP-binding cassette transporter that acts as an efflux transporter, has been shown as a target of curcumin. Recent studies indicated that curcumin inhibited the transport activity of BCRP in *in vitro* and *in vivo* animal studies [3,4]. Significantly increased plasma concentrations of sulfasalazine (SASP), an *in vivo* probe for BCRP function [5], were observed (approximately 3-folds), when curcumin was co-administrated simultaneously [6]. Mechanisms behind this interaction remains unclear, but it was reported that curcumin and curcumin analogue decreased the expression of BCRP [7-9]. Taken these findings into considerations, curcumin may cause the drug interactions with BCRP substrate drugs in humans; however, above mentioned interaction between SASP and curcumin was not observed when curcumin was given orally 4 or 5 days before administration of SASP.

Materials and Methods

Study design

This study was registered in the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/index.htm (UMIIN000009976). An open-label, single-arm and two-phase study was conducted in 34 healthy participants (age: 20-24 years; weight: 43.3-68.6 kg). Their genotyping for ABCG2 421C>A (rs2231142) polymorphisms were as following; 13 homozygotes for the wild type (C/C), 13 heterozygotes (C/A), and 8 mutant homozygotes (A/A). A single dose of SASP (2,000 mg, 4 conventional tablets of Salazopyrin®, Pfizer, Tokyo, Japan) was administered orally after overnight fast (phase 1). After seven days washout period, a single oral dose of curcumin (2,000 mg, 18 tablets, API, Gifu, Japan) was administered, and then, 4 days to 5 days after administration of curcumin, 2,000 mg of SASP was administered orally again (phase 2).

Quantification and determination of pharmacokinetic parameters of SASP in human plasma samples

Plasma concentrations of SASP were assayed by high-performance liquid chromatography, as previously described [10,11]. C_{max} and T_{max} were obtained directly from the data. The area under the plasma concentration-time curve (AUC_{0-48}) was calculated by the linear trapezoidal rule. The pharmacokinetic parameters of SASP were calculated based on non-compartmental analysis. We calculated the apparent oral clearance (CL_{tot}/F) as follows: $CL_{tot}/F=Dose/AUC_{0-48}$. We performed stratified analysis of ABCG2 421C>A polymorphism for the pharmacokinetic parameters (Table 1) [11].

Pharmacokinetic Parameters	Genotype ABCG 2	Phase 1	Phase 2
AUC_{0-48} (μg-hr/mL)	ALL	313 ± 201	314 ± 190
	CC	166 ± 76	153 ± 58
	CA	329 ± 164*	327 ± 128*
	AA	525 ± 208*, **	556 ± 144*, **
K_e (/hr)	ALL	0.09 ± 0.02	0.08 ± 0.02
	CC	0.10 ± 0.01	0.10 ± 0.02
	CA	0.08 ± 0.01*	0.08 ± 0.01*
	AA	0.07 ± 0.01*, **	0.07 ± 0.01*
Cl_{total}/F (L/hr)	ALL	8.9 ± 5.4	9.0 ± 5.8
	CC	13.9 ± 5.0	14.7 ± 5.3
	CA	6.9 ± 2.5*	6.6 ± 1.8*
	AA	4.1 ± 1.2*	3.7 ± 1.2*
$T_{1/2}$ (hr)	ALL	8.3 ± 1.5	8.5 ± 1.7
	CC	6.9 ± 0.7	7.0 ± 1.1
	CA	8.6 ± 1.0*	8.9 ± 1.2*
	AA	9.9 ± 0.9*, **	10.4 ± 0.8*, **
T_{max} (hr)	ALL	5.2 ± 1.5	5.1 ± 1.3
	CC	4.5 ± 1.1	5.2 ± 1.7
	CA	5.2± 1.8	5.1 ± 1.0
	AA	6.1 ± 1.4	5.3 ± 1.0
C_{max} (μg/mL)	ALL	24.3 ± 13.3	25.4 ± 13.2
	CC	14.8 ± 7.3	14.0 ± 6.1
	CA	26.0 ± 11.5*	27.6 ± 8.7*
	AA	37.1 ± 12.4*	40.1 ± 11.7*, **

Table 1: Pharmacokinetic parameters of SASP after oral dose of SASP with regard to the genotype of ABCG2. Each value represents the mean ± S.D. *Significantly different from values in CC subjects as determined by Tukey's test ($p<0.05$). **Significantly different from values in CA subjects as determined by Tukey's test ($p<0.05$).

Data analysis

Data are shown as means + S.D. or ± S.D. Differences between phase 1 and phase 2 were evaluated using Wilcoxon signed-rank test. Differences between three ABCG2 421C>A genotypic groups were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. Differences were considered to be significant at $p<0.05$.

Results and Discussion

Plasma concentration-time profiles of SASP in the two phases were shown in Figure 1 with regards to ABCG2 421C>A polymorphism. Pharmacokinetic parameters of SASP and influence of 421C>A polymorphism on SASP pharmacokinetics were identical between the two phases. These findings indicate that the pharmacokinetics of SASP is reproducible in the same individual, which in turn, clearly demonstrated that curcumin did not influence the pharmacokinetics of SASP in phase 2. Our previous study indicated that simultaneous administration of curcumin increased the plasma concentrations of SASP [6]. However, as shown in Figure 1, 4 to 5 days' time lag between SASP and curcumin intake disappeared such interaction.

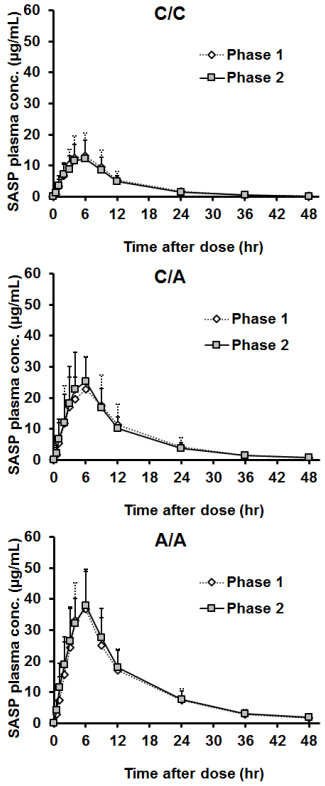

Figure 1: Effect of curcumin on plasma concentrations of SASP after oral administration of SASP tablets in three ABCG2 421C>A genotypic groups. Curcumin (2,000 mg) was given orally to healthy subjects 4 or 5 days before oral administration of conventional SASP tablets (2,000 mg). Data shown are mean (+S.D.) values of the plasma concentrations.

Since various studies showed that bioavailability of curcumin is very low (approximately 1%), concentrations of curcumin in the gastro-intestinal tracts are expected extremely high at the time of the administration. The concentration of curcumin in the small intestine reached its maximum at 0.5 hours and disappeared within 18 hours after oral administration in rats [12].

The lack of meaningful interaction with SASP may be responsible for the disappearance of curcumin in the gastro-intestinal tracts before the administration of SASP. Previously, it was reported that intestinal epithelial cells are generated by proliferating stem cells at the bottom of the Crypts of Lieberkühn [13]. During 4-5 days, intestinal epithelial cells move up towards the intestinal surface [14]. We chose a 4-5 days' time lag between the administration of curcumin and SASP to evaluate the effect of curcumin on BCRP function in the epithelial cells after the

turnover. Our results suggest that curcumin does not affect the function of BCRP after the turnover of intestinal epithelial cells. These findings specified that 4 days to 5 days time lag is necessary to avoid the drug interaction between BCRP substrates and curcumin.

In conclusion, this study demonstrated that the administration of curcumin for 4 days to 5 days prior to that of SASP had no significant effects on the pharmacokinetics of SASP. These results suggested that 4 days to 5 days' time lag is necessary to avoid the drug interaction between BCRP substrates and curcumin.

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