DOCTORAL THESIS

Mechanism of pharmacokinetic interaction between paeoniflorin and sinomenine

Liu, Zhongqiu

Date of Award:
2006

Mechanism of Pharmacokinetic Interaction between Paeoniflorin and Sinomenine

LIU Zhongqiu

A thesis submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Principal Supervisor: Dr. JIANG Zhi Hong

Hong Kong Baptist University

May 2006

ABSTRACT

Chinese medicine has been becoming more and more popular in the world. As we known, it is a common practice for Chinese medicine practitioners to prescribe herbal formula using a combination of several herbs to treat diseases. However, there is almost no detailed information and evidence of herb-herb interaction to support those combinative therapies until now. Thus, pharmacokinetic interactions of the herb-herb or compound-compound are very important and necessary to be explored, which could provide evidence to support the application of Chinese medicine.

Paeonia lactiflora Pall. root (白芍) and *Sinomenium acutum* Rehder & Wilson stem (青风藤) are two herbs widely used in Chinese medicine to treat arthritic diseases, and they are usually prescribed together in herbal formulations. Although the whole chemical profiles of these two herbs are unknown, paeoniflorin and sinomenine have been proven as the representative main bioactive constituents of *P. lactiflora* and *S. acutum*, respectively. Thus, paeoniflorin and sinomenine were employed in the current studies for investigating the pharmacokinetic interactions.

We employed an *in vivo* jugular-catheterized rat model to investigate the pharmacokinetic interactions between paeoniflorin and sinomenine. An *in vitro* everted rat gut sac technique, an *in situ* single-pass rat intestinal perfusion model, and an *in vitro* cultured Caco-2 cells model were used for investigating the mechanism of pharmacokinetic interactions between paeoniflorin and sinomenine.

The results in jugular-catheterized rat model showed that paeoniflorin has a poor bioavailability, while sinomenine has a high bioavailability. However, the

pharmacokinetic parameters of paeoniflorin (C_{max}, T_{max}, AUC, MRT, C_L and V_d) could be markedly improved when co-administrated with sinomenine, especially, the AUC of paeoniflorin were significantly elevated to 12 times, while those of sinomenine could not be altered by co-administration of paeoniflorin. After oral dosing, the concentrations of paeoniflorin in the rat internal organs were significantly increased by sinomenine, whereas those of sinomenine were not changed by paeoniflorin.

Results of the mechanistic investigation using the everted rat gut sac, the rat intestinal perfusion and the Caco-2 cells modes showed that the poor bioavailability of paeoniflorin is due to its poor permeation, the efflux via intestinal P-glycoprotein (P-gp), and hydrolytic degradation in the intestinal brush border by lactase phlorizin hydrolase. The transport and absorption of paeoniflorin in intestine can be increased by co-administration of sinomenine and P-gp inhibitors like verapamil, cyclonsporin A and quinidine, whereas its secretion can be decreased by those P-gp inhibitors, leading to elevated the blood and tissue concentrations of paeoniflorin. Sinomenine also showed significant inhibition on P-gp-mediated efflux of digoxin, a prototypical P-gp substrate.

In conclusion, there are significant pharmacokinetic interactions between paeoniflorin and sinomenine, by which the bioavailability of paeoniflorin can be markedly improved by co-administration of sinomenine. The findings can support the combinative therapy of these two chemicals as well as these two herbs. The mechanisms for the improvement of biovailability of paeoniflorin are related to the inhibition of the P-gp-mediated efflux in intestine induced by co-administration of sinomenine. Paeoniflorin was characterized as a P-gp substrate, while sinomenine was demonstrated as a P-gp inhibitor.

TABLE OF CONTENTS