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The Effects of Verapamil on the Pharmacokinetics of Paeoniflorin in Rats

Lu LIU [1 #], Xiaohua LI [1 #], Yawei YUAN [2 #] & Pihong LI [3 *]

[1] *Department of Endocrinology, Seventh People's Hospital of Shanghai University of TCM, Shanghai 200137, China*

[2] *Department of Anesthesiology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China*

[3] *Department of General Surgery, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China*

***SUMMARY*. Paeoniflorin, a Chinese herbal medicine, has been widely used in clinical practice in China because of its numerous pharmacological activities. This study investigates the effects of verapamil on the pharmacokinetics of paeoniflorin in rats and clarify its potential mechanism. First, the pharmacokinetics of paeoniflorin (20 mg/kg) in rats with or without pretreatment with verapamil (10 mg/kg) were determined using a sensitive and reliable LC-MS method. Then the effects of verapamil on the transport and metabolic stability of paeoniflorin were investigated using Caco-2 cell transwell model and rat liver microsome incubation systems. The results showed that verapamil could significantly increase the peak plasma concentration (from 137.68 ± 12.48 to 185.25 ± 21.01 ng/mL) and AUC_{0-t} (from 990.35 ± 110.25 to 1472.48 ± 243.52 ng.h/mL) of paeoniflorin. The Caco-2 cell experiments indicated that the efflux ratio of paeoniflorin was 2.90 (P_{appAB} 6.35 ± 0.52 × 10^{-7}; P_{appBA} 1.84 ± 0.32 × 10^{-6} cm/s), *P-gp* might be involved in the transport of paeoniflorin, and verapamil could inhibit the efflux of paeoniflorin and increase the absorption of paeoniflorin significantly in the Caco-2 cell monolayer. Additionally, the rat liver microsome incubation experiments indicated that verapamil could significantly increase the metabolic stability of paeoniflorin from 31.5 to 46.8 min. Those results indicated that verapamil could significantly change the pharmacokinetic profiles of paeoniflorin in rats, the poor absorption due to *P-gp* mediated efflux in intestine and high intrinsic clearance rate in rat liver may be the main reason for its poor oral absolute bioavailability of paeoniflorin.**

RESUMEN. Paeoniflorina, una medicina herbal china, ha sido ampliamente utilizada en la práctica clínica en China debido a sus numerosas actividades farmacológicas. Este estudio investiga los efectos del verapamil en la farmacocinética de paeoniflorina en ratas y aclara su mecanismo potencial. Primero, se determinó la farmacocinética de paeoniflorina (20 mg/kg) en ratas con o sin tratamiento previo con verapamil (10 mg/kg) utilizando un método LC-MS sensible y confiable. Luego se investigaron los efectos del verapamil en el transporte y la estabilidad metabólica de paeoniflorina utilizando el modelo de transwell de células Caco-2 y los sistemas de incubación de microsomas de hígado de rata. Los resultados mostraron que el verapamil podría aumentar significativamente la concentración plasmática máxima (de 137.68 ± 12.48 a 185.25 ± 21.01 ng/mL) y el AUC_{0-t} (de 990.35 ± 110.25 a 1472.48 ± 243.52 ng.h/mL) de paeoniflorina. Los experimentos con células Caco-2 indicaron que la proporción de eflujo de paeoniflorina fue de 2.90 (P_{appAB} 6.35 ± 0.52 × 10^{-7}; P_{appBA} 1.84 ± 0.32 × 10^{-6} cm/s), *P-gp* podría estar involucrada en el transporte de paeoniflorina, y verapamil podría inhibir la salida de paeoniflorina y aumentar su absorción de manera significativa en la monocapa de células Caco-2. Además, los experimentos de incubación de microsomas de hígado de rata indicaron que verapamil podría aumentar significativamente la estabilidad metabólica de paeoniflorina de 31.5 a 46.8 min. Esos resultados indicaron que verapamil podría cambiar significativamente los perfiles farmacocinéticos de paeoniflorina en ratas. La mala absorción debida al flujo mediado por *P-gp* en el intestino y la alta tasa de aclaramiento intrínseco en el hígado de ratas puede ser la razón principal de la escasa biodisponibilidad oral absoluta de la paeoniflorina.

KEY WORDS: Caco-2 cells, CYP450, oral absolute bioavailability, paeoniflorin, *P-gp,* verapamil.

# These authors contributed equally to this work.
* Author to whom correspondence should be addressed. *E-mail:* lipihong08@163.com

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