

A Commentary on Influence of Traditional Chinese Medicines on the *In vivo* Metabolism of Lopinavir/ritonavir Based on UHPLC-MS/MS Analysis

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Commentary

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ABOUT THE STUDY

Since the outbreak of the epidemic situation of novel coronavirus (COVID-19), it has caused a large number of morbidity and mortality cases around the world. The clinical practice has proved that the combination of traditional Chinese medicine and chemical medicine played an important role in rapidly inhibiting virus replication, alleviating patients' clinical symptoms and reducing adverse reactions. In the process of drug combination, the traditional Chinese medicine preparation may affect the drug metabolism enzymes, transporters and the internal microenvironment (pH, electrolyte, intestinal flora, etc.), change the internal metabolism (kinetics) of chemical medicine, and lead to the decline of drug efficacy and the aggravation of adverse reactions.

Kaletra (lopinavir/ritonavir) has been continuously recommended as an anti COVID-19 virus drug in Chinese COVID-19 diagnosis and treatment program (Version 3-8), and was often used in combination with Lianhua Qingwen granules and other traditional Chinese medicine preparation, which has played an important role in rapidly curbing the epidemic in China. A fast, reliable and sensitive LC-MS/MS method was established by the research group to determine the effects of traditional Chinese medicine for COVID-19 namely Lianhua Qingwen granules, Huoxiang Zhengqi capsules, Jinhua Qinggan granules, Shufeng Jiedu capsules and Angong Niu Huang pills on the pharmacokinetic of lopinavir/ritonavir in rats.

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In this method, the blood samples were prepared by protein precipitation with atazanavir as an Internal Standard (IS), and the separation was performed on an Agilent ZORBAX eclipse plus C18 column with acetonitrile and water-0.1% formic acid by gradient elution. Agilent Jet Stream Electrospray Ionization (AJSESI) was used for mass spectrometry detection under positive ion Multiple Reaction Monitoring (MRM) mode at transition of m/z 629.3→447.3 for lopinavir, m/z 721.32→96.1 for ritonavir and m/z 705.4→168.1 for IS. All the validation indicators of analytical methodology were within the acceptable range. The pharmacokinetic results showed that the $t_{1/2}$ of ritonavir in Lianhua Qingwen Granules, Huoxiang Zhengqi Capsules combined with lopinavir /ritonavir group was prolonged about 1.5~2 times compared with the control group. Similarly, the pharmacokinetic parameters of lopinavir also changed significantly.

The reasons for the change of the pharmacokinetic parameters of lopinavir/ritonavir were also discussed in the article, took the Lianhua Qingwen granules as an example, it mainly contain *Forsythia*, *Honeysuckle*, *Radix isatidis*, and *Ephedra sinica*. Previous studies have reported that *Forsythia* can induce the expression of P-gp and drug metabolism enzymes, such as CYP3A4, CYP2C9, and CYP2C19 in the intestine and liver. Therefore, the change in the pharmacokinetic parameters of this group was speculated to be caused by the induction of CYP3A4 expression by *Forsythia*, which resulted in a decrease in the AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} of lopinavir, and an increase in CL/F .

The results of this study can provide important theoretical parameters for the clinical rational use of five kinds of traditional Chinese medicine combined with lopinavir/ritonavir, so as to reduce the occurrence of clinical adverse reactions and improve drug efficacy. The pharmacokinetic characteristics of lopinavir and ritonavir in rat plasma were examined using an HPLC-MS/MS method to assess the impact of five TCMS. The developed technique offered the following benefits: great selectivity, high sensitivity, high reproducibility, quick sample processing, and simple operation.