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# PHARMACOKINETIC INTERACTION OF HERBS AND DRUGS BETWEEN ICOTINIB AND TETRANDRINE (Tet) IN RATS

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**Abstract:**

*To investigate the effects of tetrandrine (Tet) on the pharmacokinetics of icotinib, twelve male rats were randomly divided into two groups (n = 6). Experimental group and control group were pretreated with Tet or saline once a day by oral administration for 10 days in a row. Then, icotinib (35mg/kg) were given to all rats orally on the 11th day. Blood samples were collected from the tail vein and the plasma concentrations of icotinib were detected by Ultra Performance Liquid Chromatography-tandem Mass spectrometric (UPLC) method. The pharmacokinetic parameters of cortisol in the experimental group and contral group were: 10.3 ± 3.9 and 7.3 ± 2.7 h for t1/2z; 1.4 ± 0.5 and 0.7 ± 0.2 L/h/kg for CL/F; 26873.8 ± 8439.7 and 55472.6 ± 18997.9 μg/L.h for AUC(0-t); 27069.4 ± 8609.9 and 55563.5 ± 18987.1 μg/L.h for AUC(0-∞); (6379.4 ± 1230.5) and 11612.9 ± 3125.7 h for Cmax; 1.6 ± 0.4 and 0.7 ± 1.0 h for Tmax, respectively. Those results indicated that the Tet can induce icotinib metabolism significantly in rats, which may be related to its induction effect on CYP450.*

*RESUMEN. Para investigar los efectos de la tetrandrina (Tet) en la farmacocinética de icotinib, doce ratas macho se dividieron aleatoriamente en dos grupos (n = 6). El grupo experimental y el grupo de control se pretrataron con Tet o solución salina una vez al día mediante administración oral durante 10 días seguidos. Luego, se administró icotinib (35 mg/kg) a todas las ratas por vía oral el día 11º. Las muestras de sangre se tomaron de la vena de la cola y las concentraciones plasmáticas de icotinib se detectaron mediante el método de espectrometría de masas en tándem con cromatografía líquida de ultra performance (UPLC). Los parámetros farmacocinéticos del cortisol en el grupo experimental y el grupo contral fueron: 10.3 ± 3.9 y 7.3 ± 2.7 h para t1/2z, 1.4 ± 0.5 y 0.7 ± 0.2 L/h/kg para CL/F, 26873.8 ± 8439.7 y 55472.6 ± 18997.9 μg/L para AUC (0-t), 27069.4 ± 8609.9 y 55563.5 ± 1 8987.1 μg/L para AUC(0-∞), 6379.4 ± 1230.5 y 11612.9 ± 3125.7 h para Cmax y 1.6 ± 0.4 y 0.7 ± 1.0 h para Tmax, respectivamente. Esos resultados indicaron que el Tet puede inducir el metabolismo de icotinib significativamente en ratas, lo que puede estar relacionado con su efecto de inducción en CYP450.*

*KEY WORDS : icotinib , pharmacokinetics , tetrandrine , UPLC-MS/MS.*

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## INTRODUCTION:

Non-small-cell lung cancer (NSCLC) is one type of epithelial lung cancer and accounts for more than 80% of all lung cancers cases 1,2. Epidermal pidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been widely used in the treatment of NSCLC patients with sensitive EGFR mutations, such as erlotinib, gefitinib, afatinib and osimertinib. Icotinib is chemically synthesized for the treatment of NSCLC by Zhejiang Beta Pharma Co. Ltd. (Zhejiang, China) as an oral and novel EGFR-TKI. Icotinib monotherapy is an effective and well tolerated regimen for Chinese patients with NSCLC after the failure of chemotherapy. But, some articles reported that icotinib resistance is happened to EGFR-mutant NSCLC patients 3,4. Radiation combined with targeted therapy is the focus of research in recent years 5. The treatment modality of continued EGFR-TKI with concurrent radiotherapy (CTCRT) is considerable and effective for EGFR-mutant NSCLC patients even with local failure from front-line EGFR-TKI treatment 6. In the last couple of years, many TCMs have been approved by the Chinese State Food and Drug Administration and used for the treatment of some tumors, including NSCLC 7-12. Tetrandrine (Tet) is a bisbenzylisoquinoline alkaloid extracted originally from the root of Stephania tetrandra S. Moore and has been widely used in the clinical treatment of rheumatism and silicosis in china 13. Recently, the anti-tumor effects of tetrandrine have been widely investigated 14,15. Moreover, Ye et al. 16 found that Tet is a potent autophagy agonist and may be a promising drug for the treatment of NSCLC. More impressive is that Tet is a potential radiosensitizer 17,18 and also a multidrug resistance reversing agent in various cancer cells 19-22. Thus, Tet can be taken priority in clinical adjuvant drug use for NSCLC. As it is known, drug combination would strengthen or weaken the drug action, even lead to unexpected adverse drug reaction. To date, systematic studies on the pharmacokinetic drugdrug interaction of icotinib were limited. About the effects of Tet, however, there is still little information on the pharmacokinetics of icotinib in vivo. Therefore, we investigated the effects of Tet on the pharmacokinetics of icotinib in rats in this study.

## MATERIALS AND METHODS:

Chemicals and reagents Tet was a gift from Zhejiang Conba Pharmaceutical Co., Ltd (Zhejiang, China). Icotinib hydrochloride (purity 98%) and internal standard (IS) imatinib were got from the Zhejiang Bata Pharma Inc (Zhejiang, China) and the National Institute for Control of Pharmaceutical and Biological Products (Beijing, China), respectively. Acetonitrile and methanol were purchased from Merck Company (Darmstadt, Germany). All other chemicals and solvents used were of analytical grade or chemical grade. Ultra-pure water prepared by a Millipore Milli-Q purification system (Bedford, MA, USA) was used for making mobile phase.

### Animals

The Sprague-Dawley male rats (290 ± 20 g) were obtained from Laboratory Animal Center of Wenzhou Medical University (Wenzhou, China). The rats were acclimatized for a week to laboratory conditions before initiating the experiment. Necessary approval from the Institutional Animal Ethics Committee of Wenzhou Medical University was obtained to carry out the experiment.

### Pharmacokinetic Experiment

Twelve rats were randomly divided into 2 groups (n = 6): control group and experimental group. Water was freely accessible 12 h before experiment but no food was allowed. These rats in experimental group were respectively given 20 mg/kg Tet for 10 consecutive days by oral administration, while the control group was orally given normal saline. After the last administration of Tet or saline on the 11th day, each rat in two groups was orally treated with icotinib (35 mg/kg), which was dissolved in 0.5% sodium carboxymethyl cellulose (CMC-Na). Blood samples (0.2 mL) were directly collected into a clean tube from the tail vein at the time points of 0 (prior to dosing), 0.083, 0.333, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0, and 48.0 h after administration and plasma samples were harvested by centrifuging at 3000 rpm for 10 min and stored at -20 °C until bioanalysis.

### Sample Preparation

Before analysis, the plasma samples were thawed to room temperature. In a 1.5 mL centrifuge tube, an aliquot of 150 µL acetonitrile (containing 50 ng/mL of IS) was added to 50 µL of collected plasma sample. These tubes were mixed for 1.0 min in a vortex finder and centrifuged at 13000 rpm for 10 min. A 2 µL aliquot of the final supernatant was injected into the UPLC-MS/MS system for analysis.

### Instrumentation and conditions

Liquid chromatography was performed on an ACQUITY I-Class ultra performance liquid chromatography (UPLC) unit (Waters Corp., Milford, MA) with an UPLC BEH C18 column (2.1 × 50 mm, 1.7 µm particle size). A gradient program was employed with the mobile phase combining solvent A (0.1% formic acid in water) and solvent B (acetonitrile) as follows: 0~0.2 min, 10% B; 0.2-1.5 min, 10~75% B; 1.5-2.0 min, 75% B; 2.0-2.5 min, 75~10% B; 2.5-4.0 min, 10% B. The flow rate was 0.40 mL/min and the injection

volume was 2 µL. The column and sample temperature were maintained at 40 and 4 °C, respectively. A XEVO TQS-micro triple quadrupole mass spectrometer (Waters Corp., Milford, MA, USA) equipped with an electrospray ionization (ESI) interface in the positive ion mode was used for mass spectrometric detection. Data acquiring and processing were performed using Masslynx 4.1 software (Waters Corp.). The Multiple Reaction Monitoring (MRM) mode was applied to monitor icotinib ions at m/z 392.2→304.3. The cone voltage for icotinib was set at 30 V and the collision voltage was set at 25 V. For IS, m/z 494.2→394.3 with a cone voltage of 35 V and a collision voltage of 26 V. The main working parameters of the mass spectrometer are as follows: Nitrogen was used as the desolvation gas (800 L/h) and cone gas (50 L/h). Capillary voltage was set at 2.2 kV; The source temperature and desolvation temperature were 150 and 400 °C, respectively.

**Statistical Analysis**

Experimental values are expressed as mean ± SD. These main parameters of each group contain half-life (t1/2), total body clearance (CL), the area under the concentration-time curve (AUC(0-t), AUC(0-∞)) and the maximum plasma concentration (Cmax). Statistical analyses of main pharmacokinetic parameters were performed by Student's test using SPSS 16.0 software. A value of $P < 0.05$ was considered to be significant between two groups.

**RESULTS:**

Method validation A UPLC method for the determination of icotinib in rat plasma was improveed and validated based on our previous report 23. As shown in Fig. 1, icotinib and IS were eluted at about 1.72 Figure 1. Representative chromatograms of icotinib and IS in rat plasma samples. (A) a blank plasma sample; (B) a rat plasma sample after oral administration of 35.0 mg/kg icotinib. and 1.59 min, respectively. The internal standard and resolution of icotinib was satisfactory for no interference in the chromatograms. The lower limit of quantification (LLOQ) was 1 ng/mL. Calibration curves were linear over the range of 1-2000.0 ng/mL, the linear regression equation was y = 0.000445 x - 0.000438 (r = 0.99992). And the accuracy and the precision were both less than 15.0%. The recovery of icotinib was above 62.1%, and matrix effects were between 104.3 and 108.8%. Thus, the validate method was accurate and meets the requirement of high sample throughput in bioanalysis, and has been successfully applied to the pharmacokinetic study of icotinib in rats.

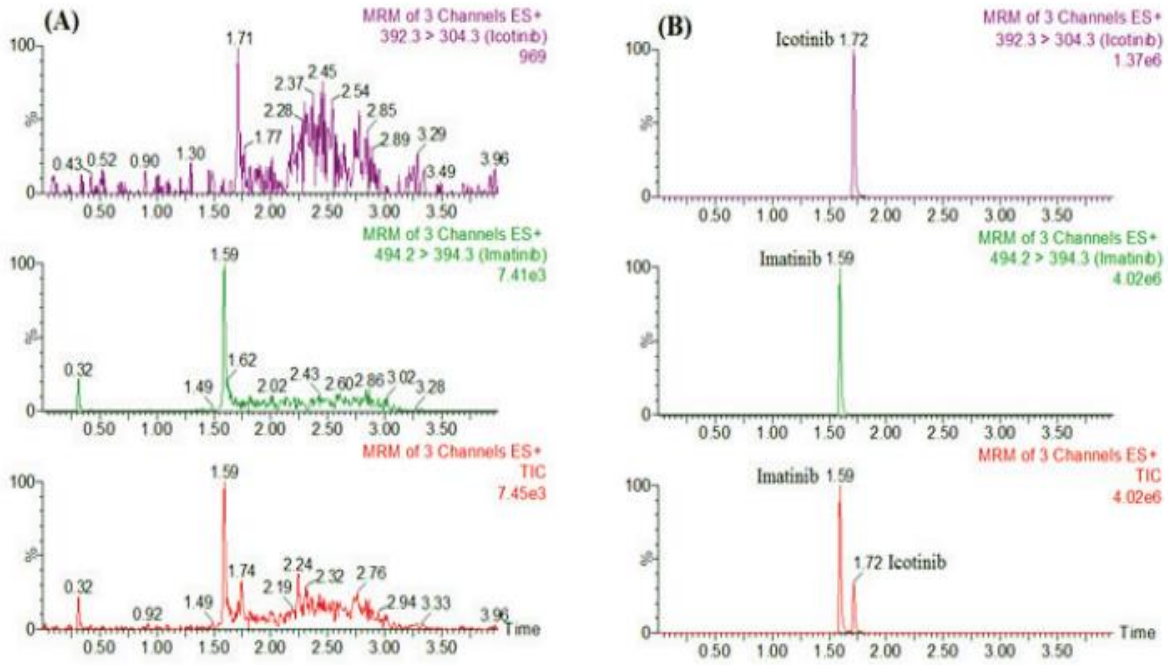


**Figure 1**. Representative chromatograms of icotinib and IS in rat plasma samples. (**A**) a blank plasma sample; (**B**) a rat plasma sample after oral administration of 35.0 mg/kg icotinib.

| Pharmacokinetic parameters | Unit | Experimental group | Control group |
|---|---|---|---|
| $AUC_{(0-t)}$ | ng/mL.h | 26873.8 ± 8439.7* | 55472.6 ±18997.9 |
| $AUC_{(0-\infty)}$ | ng/mL.h | 27069.4 ± 8609.9* | 55563.5 ±18987.1 |
| $MRT_{(0-t)}$ | h | 4.0 ± 1.4 | 4.2 ± 1.0 |
| $MRT_{(0-\infty)}$ | h | 4.3 ± 1.8 | 4.3 ± 1.0 |
| $t_{1/2z}$ | h | 10.3 ± 3.9 | 7.3 ± 2.7 |
| $T_{max}$ | h | 1.6 ± 0.4 | 0.7 ± 1.0 |
| $CL_{z/F}$ | L/h/kg | 1.4 ± 0.5* | 0.7 ± 0.2 |
| $V_{z/F}$ | L/kg | 20.1 ± 8.6* | 7.6 ± 4.3 |
| $C_{max}$ | ng/mL | 6379.4 ± 1230.5* | 11612.9 ± 3125.7 |

**Table 1**. The pharmacokinetic parameters of icotinib in experimental group and contral group. *Significant difference ($p < 0.05$) in comparison with control group.

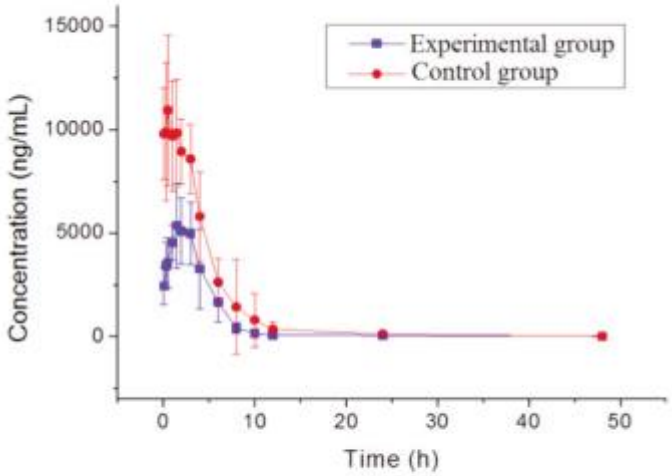


**Figure 2**. Mean concentration-time curve of icotinib in two groups after oral administration of TET (n=6).

**Effect of Tet on pharmacokinetics of icotinib**

The data of pharmacokinetic parameters of icotinib were calculated using method of the non-compartmental model with DAS 2.0 software. The mean concentration-time curves of icotinib in two groups were presented in Fig. 2, and the pharmacokinetic parameters were presented in Table 1. The results showed the AUC(0-t) in experimental group decreased by 51.6% ($p < 0.05$), Cmax decreased by 45.1% ($p < 0.05$), t1/2z increased by 41.1% ($p > 0.05$), tmax increased by 1.3 times ($p > 0.05$) and CLz/F doubled ($p < 0.05$) compared with the control group.

## DISCUSSION:

Treatment failure and adverse drug reactions frequently caused by drug-drug interactions. Besides cellular efflux, drug metabolism/degradation is thought to be another important factor affecting pharmacokinetics of drugs 24. Recently, the interactions between traditional Chinese medicines (TCM) and drugs had been reported more and more 25-27. When patients use Chinese herbs and western drugs together, the probability of herb-drug interactions will be increased, because the complex ingredients in herbs may share the same metabolic enzyme and transport proteins with chemical medicines. Tet could be frequently combined with other drugs because it has numerous pharmacological activities and is a potential multidrug resistant modulator. DDI between Tet and other drugs may cause the risk of either diminished efficacy or adverse effects. Our results showed that the most of pharmacokinetic profiles of icotinib were changed by Tet ($p < 0.05$), indicating that the icotinib metabolism in rats can be induced by TET significantly. For the possible use of TET and icotinib among NSCLC patients, our results provide cues that when icotinib and TET are combined to treat patients, dosage adjustment and care should be taken. Cytochrome P450 enzymes

(CYPs) play a significant role in drug-drug interactions and herb-drug interplays 28. As we all known, induction of CYP450s can lead to decreased plasma levels of drugs which can reduce the effectiveness of drugs. The CYP2C19, CYP3A4 and CYP1A2 are the main enzymes involved in the metabolism of icotinib 29,30. These findings offer a clear understanding that the potential DDI between icotinib and CYP3A4/5 inhibitors or inducers may occur in clinic. Thus, we speculated that the change of pharmacokinetics of icotinib in treatment group is attributable to the inductive effect of Tet on CYPs activity, especially on 3A4. Moreover, further research should be conducted for the effect of Tet on CYPs activities in vivo is still unreported.

## CONCLUSION:

The present results demonstrate that Tet can alter the pharmacokinetic characteristics of icotinib after combined delivery, which means Tet can induce the metabolism of icotinib in vivo with potential clinical significance. When combined use of TET and icotinib, we should pay attention to the dose adjustment to avoid treatment failure. This experiment is the initial result of the animal experiment, only as the reference of clinical medication. The definite mechanisms of this effect and the pharmacokinetics of the two drugs in the human body remains to further study

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