Effects of dacomitinib on the pharmacokinetics of poziotinib in vivo and in vitro

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ABSTRACT

Context: Dacomitinib and poziotinib, irreversible ErbB family blockers, are often used for treatment of non-small cell lung cancer (NSCLC) in the clinic.

Objective: This study investigates the effect of dacomitinib on the pharmacokinetics of poziotinib in rats.

Materials and methods: Twelve Sprague–Dawley rats were randomly divided into two groups: the test group (20 mg/kg dacomitinib for 14 consecutive days) and the control group (equal amounts of vehicle). Each group was given an oral dose of 10 mg/kg poziotinib 30 min after administration of dacomitinib or vehicle at the end of the 14-day administration. The concentration of poziotinib in plasma was quantified by UPLC-MS/MS. Both in vitro effects of dacomitinib on poziotinib and the mechanism of the observed inhibition were studied in rat liver microsomes and human liver microsomes.

Results: When orally administered, dacomitinib increased the AUC, \( T_{\max} \) and decreased CL of poziotinib (\( p < 0.05 \)). The \( IC_{50} \) values of M1 in RLM, HLM and CYP3A4 were 11.36, 30.49 and 19.57 \( \mu M \), respectively. The \( IC_{50} \) values of M2 in RLM, HLM and CYP2D6 were 43.69, 0.34 and 0.11 \( \mu M \), respectively, and dacomitinib inhibited poziotinib by a mixed way in CYP3A4 and CYP2D6. The results of the in vivo experiments were consistent with those of the in vitro experiments.

Conclusions: This research demonstrates that a drug–drug interaction between poziotinib and dacomitinib possibly exists when readministered with poziotinib; thus, clinicians should pay attention to the resulting changes in pharmacokinetic parameters and accordingly, adjust the dose of poziotinib in clinical settings.

Introduction

The tyrosine kinase inhibitor (TKI) family is a family of oral epidermal growth factor receptor drugs that inhibit the activity of tyrosine kinase. This family can be roughly divided into three types, reversible EGFR-TKIs (such as erlotinib and gefitinib), irreversible ErbB family blockers (poziotinib and dacomitinib) and mutant-selective EGFR-TKIs (AZD9291, CO-1686 and HM6171) (Leong et al. 2017; Koga et al. 2018; Belgin et al. 2019; Kim Y et al. 2019). Dacomitinib is representative of highly selective reversible EGFR-TKIs, including HER1, HER2 and HER4 (Qiu et al. 2019). It has previously been reported that dacomitinib has a significant therapeutic effect on patients with advanced non-small cell lung cancer (NSCLC) with EGFR-activating mutations, gastric cancer and neck squamous cell carcinoma (Abdul Razak et al. 2013; Oh et al. 2016; Kim DW et al. 2017). In addition, Yu et al. (2019) observed that dacomitinib reduces pulmonary artery pressure and relieves right ventricular hypertrophy. Several previous experiments have indicated that dacomitinib is mainly mediated by CYP2D6 and, to a lesser extent, by CYP3A4 and CYP2C9 (Peters et al. 2014; Giri et al. 2015; Chen et al. 2018). Additionally, dacomitinib is a substrate for CYP2D6 and an inhibitor of CYP2D6. The metabolism of dacomitinib varies across different ethnic groups and foods (Ramalingam et al. 2014). Research by Bello et al. (2012) indicated that the combined use of dacomitinib and the drug metabolized by CYP2D6 can have a significant impact on the pharmacokinetics of subjects with an extensive metabolism for CYP2D6. An experiment Ruiz-Garcia et al. (2014) discovered that, when coadministered with paroxetine, which is a potent CYP3A4 inhibitor, dacomitinib exposure increased by 37% in healthy volunteers. When taken every day, the modest effect of dacomitinib is unlikely to be clinically significant.

Poziotinib (HM781-36B) is a novel oral irreversible panhuman EGF receptor (HER) TKI, and it has a stronger inhibitory effect on EGFR than that of other EGFR tyrosine kinase inhibitors, including EGFR-acquired resistance mutation (T790M), HER2 and HER4 (Nam et al. 2011). Poziotinib is clinically used...
for treating a variety of advanced solid tumours, including non-small cell lung cancer (NSCLC) with EGFR mutations (T790M), breast cancer, and gastric cancer (Cha et al. 2012; Park et al. 2018; Kim JY et al. 2019). Kim et al. (2013) reported that HM781-36B is mainly metabolised by CYP3A4 (mainly M1) and partially metabolized by CYP2D6 (mainly M2), which they determined via in vitro and in vivo experiments (Figure 1). In other words, using the representative HPLC chromatograms of HM781-36B incubation products in HLM, human recombinant CYP3A4, and CYP2D6 at 254 nm, they concluded that the main metabolites of HM781-36B were M1, M2, M8 and M10 and the minor metabolites of HM781-36B were M3, M4, M5, M6, M7 and M9. Noh et al. (2015) demonstrated that, aside from weight, HM781-36 pharmacokinetics were not affected by other patient factors (including sex, height medical history, tumour types, etc.). Although, in their study, HM781-36 was administered regardless of food intake, no study has been performed on the effect of drugs on HM781-36. Considering the pharmacokinetic characteristics of dacomitinib and poziotinib, we hypothesize that when dacomitinib is administered for several days prior to taking poziotinib, the metabolism of poziotinib in vivo may be altered. The effect may be increased adverse reactions, such as diarrhoea, stomatitis, cheilitis, conjunctivitis and anorexia (Kimura et al. 2017; Kim et al. 2018).

The purpose of this experiment was to investigate the effects of dacomitinib on the pharmacokinetics of poziotinib in vivo and in vitro. The pharmacokinetic parameters of poziotinib in rats with or without dacomitinib pre-treatment were analyzed using a sensitive and reliable UPLC-MS/MS system in vivo. The effect of dacomitinib on poziotinib in rat liver microsomes was determined. Additionally, the peak areas of the two major metabolite products (M1 and M2) of poziotinib were measured in vitro (Noh et al. 2015; Cheong et al. 2017).

Materials and methods

Chemicals and reagents

Dacomitinib (purity > 98%), poziotinib (purity > 98%) and enasidenib (purity > 98%) were purchased from the Beijing Sunflower and Technology Development Co. Ltd. (Beijing, China). Acetonitrile and methanol were purchased from Fisher Scientific Co. (Fair Lawn, NJ, USA). Formic acid was purchased from Sigma-Aldrich (St. Louis, MO, USA). Ultrapure water was obtained from a Milli-Q water purification system (Millipore, Billerica, MA, USA). Carboxy methylcellulose sodium salt (CMC-Na) was from Sinopharm Chemical Reagent Co. Ltd (Shanghai China). Food was purchased from Shenyang Maohua Biotechnology Co. Ltd (Shenyang China). The reduced form of nicotinamide adenine dinucleotide phosphate was purchased from Roche Co. Ltd (Shanghai, China). HLM were purchased from Corning Co. Ltd (Woburn, MA, USA). All other chemicals were of analytical grade or better.

Instruments and conditions

The concentrations of poziotinib were determined on a UPLC-MS/MS system, which possessed an ACQUITY I Class UPLC and a XEVO TQD triple quadrupole mass spectrometer (Waters Corp., Milford, MA, USA). The UPLC system consists of a Binary Solvent Manager (BSM) and a Sample Manager with Flow-Through Needle (SM-FTN). Chromatographic analysis of poziotinib was performed on a CORTECS C18 column (2.1 × 50 mm, 1.6 μm) maintained at 40 °C. The mobile phase consisted of 0.1% formic acid and acetonitrile, and the elution process had a linear gradient: It started with acetonitrile...
increasing from 10 to 30% (0–1 min); rapidly increasing from 30 to 95% (1–2 min), which was maintained at 95% (2–2.5 min); and then decreasing to 10% (2.5–2.6 min). The flow rate was 0.4 mL/min, and the total run time was 3 min. The precursor ion and product ion, which were determined by the positive MRM mode, were m/z 492.06→354.55 and m/z 474.57→456.64 for poziotinib and IS, respectively. The optimal MS parameters were defined as follows: the cone voltages were both set at 30 V for poziotinib and IS; the collision energies were set at 20 and 28 eV for poziotinib and IS, respectively.

**Animals and treatment**

Sprague–Dawley rats were obtained from the experimental animal centre of Wenzhou Medical University (Wenzhou China). The animals were housed in a breeding room at 25°C with 60 ± 5% humidity and a 12 h dark/light cycle. Water and diet were provided ad libitum. The Sprague–Dawley rats were acclimated to the above conditions for two weeks before initiating the animal experiment. All of the experimental procedures were approved by the Animal Experimental Ethical Inspection of Laboratory Animal Centre, Wenzhou Medical University and followed the guidelines for the care and use of laboratory animals (ID Number: wydw2019-650).

**Pharmacokinetic experiment**

Twelve Sprague–Dawley rats weighing 240 ± 10 g were selected and divided into two groups (n = 6). The groups were as follows: the control group and the test group. First, dacomitinib was dissolved in a CMC-Na solution. Then, 20 mg/kg/day dacomitinib was orally administered once daily to the test group for two weeks, while equal amounts of vehicle (normal CMC-Na solution) were orally administered to the control group. Thirty minutes later, each group of rats was given an oral dose of 10 mg/kg poziotinib (dissolved in CMC-Na solution) at the end of the 14 day administration. A 50 µL aliquot of blood was collected from the rat tail vein at 0.167, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 36 h after poziotinib administration. To the collected blood, 20 µL of IS and 100 µL of acetonitrile were added in a 1.5 mL microcentrifuge tube. The mixture was vortexed for 30 s and centrifugation at 13,000 rpm for 5 min. Subsequently, the supernatants were removed and placed in a sample bottle. Supernatant (5 µL) was immediately analysed using a sensitive and reliable LC-MS/MS method.

**In vitro experiments**

The procedure for preparing RLM was based on the methods of Marques et al. (2014). The 200 µL incubation system contained 2 µM poziotinib; 0.44 mg/mL RLM, 5 pmol recombinant human CYP3A4 or 5 pmol recombinant human CYP2D6; 1 mM NADPH; and 100 mM potassium phosphate buffer (pH 7.4) and dacomitinib. To determine the IC50 of dacomitinib for inhibiting poziotinib metabolism, the concentration of dacomitinib was set as 0.01, 0.1, 1, 5, 10, 50 and 100 µM, while that of poziotinib was 100 µM for 0.44 ng/mL RLM, 0.28 mg/mL HLM, 5 pmol recombinant human CYP3A4 or 5 pmol recombinant human CYP2D6, which was close to its Km value. To determine the mechanisms underlying the inhibitory effect of dacomitinib on poziotinib metabolism on the basis of the IC50 and Km value, 0, 5, 10, 20, 50 and 100 µM of dacomitinib, and 1, 2.5, 5, 10 and 20 µM of poziotinib were selected in the RLM system; 0, 7.5, 15, 30 and 60 µM of dacomitinib, and 1, 2.5, 5 and 10 µM of poziotinib were selected in the HLM system.

The incubation was performed at 37°C for 50 min, followed by cooling to −80°C to terminate reaction at the same time, after which 400 µL of acetonitrile and 20 µL of IS (50 ng/mL) were added to the mixture. After vortex mixing for 30 s and centrifugation, 100 µL of the supernatant was obtained for LC-MS/MS analysis.

**Statistical analysis**

The pharmacokinetic parameters, including the maximal plasma concentration (Cmax), the maximum plasma time (Tmax), the apparent volume of distribution (Vz/F), the area under the plasma concentration-time curve (AUC), the elimination half-life (t1/2), the plasma clearance (CL) and the mean residence time (MRT), were analyzed using DAS (Drug and Statistics) software (Version 3.2.8, The People’s Hospital of Lishui, China). The IC50 and Lineweaver–Burk plot were obtained using GraphPad Prism (Version 7; GraphPad Software Inc., San Diego, CA, USA).

All of the pharmacokinetic parameters are expressed as the mean ± SD. Statistical analyses of the main pharmacokinetic parameters were performed using the independent sample Student’s t-test using SPSS (version 16.0; SPSS Inc., Chicago, IL, USA). Values of p < 0.05 were considered to be statistically significant.

**Results**

**Method validation and LC-MS/MS**

The validation procedures for selectivity, linearity, accuracy, precision, recovery and stability referred to the European Medicines Agency Guidelines and US-FDA Bioanalytical Method Validation Guidance (Ma et al. 2015; Wang SH et al. 2015, 2016; Wang XQ et al. 2015; Kaza et al. 2019). The inter- and intraday precision, accuracy, recovery and matrix of poziotinib in rat plasma are shown in Table 1. The chromatograms of a blank plasma sample, a blank plasma sample added to poziotinib (LLOQ) and IS, and a plasma sample after the oral administration of poziotinib are shown in Figure 2. The concentrations of the calibration curves ranged from 1 to 1000 ng/mL for poziotinib, with both correlation coefficients over 0.9907. The LLOQ was set at 1 ng/mL for poziotinib with acceptable accuracy and precision.

| Table 1. Inter- and intraday precision, accuracy, recovery and matrix of poziotinib in rat plasma (n = 6, mean ± SD). |
|---|---|---|---|
| **Nominal concentration (ng/mL)** | **Intraday Precision (%)** | **Intraday Accuracy (%)** | **Interday Precision (%)** | **Interday Accuracy (%)** | **Recovery (%)** | **Matrix (%)** |
| **Poziotinib** | | | | | | |
| 1 | 14.00 | 106.42 | 9.85 | 102.54 | 81.80 | 85.36 |
| 2 | 7.47 | 108.44 | 8.67 | 109.38 | 96.42 | 87.71 |
| 80 | 7.77 | 106.84 | 5.27 | 105.72 | 96.42 | 87.71 |
| 800 | 6.49 | 107.46 | 9.52 | 102.62 | 93.58 | 91.94 |
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The mean plasma concentration-time curves of poziotinib in the test (preadministered dacomitinib) and control (equal amounts of vehicle) groups are shown in Figure 3. Comparing the test group with the control group, the AUC(0–t) of poziotinib was increased by 1.6-fold, and the difference was significant (p < 0.01). When preadministered with dacomitinib (10 mg/kg) for two weeks, the Tmax and t1/2 values of poziotinib were significantly increased by 1.3- and 1.6-fold, respectively. Compared with the control group, the values of MRT(0–t), MRT(0–∞) and AUC(0–∞) of poziotinib were increased while the value of CLz/F was decreased. The Cmax and Vz/F values of poziotinib were not greatly changed by pre-treatment with dacomitinib (p > 0.05).

Effects of dacomitinib on the pharmacokinetics of poziotinib in vitro

Michaelis–Menten kinetics of poziotinib in RLM and HLM were shown in Figure 4. The inhibitory effect of dacomitinib on poziotinib in RLM, HLM, CYP2D6 and CYP3A4 were investigated according to the peak area ratio of metabolites of poziotinib (M1 and M2). The IC50 values of poziotinib are shown in Figure 5. The mechanism of inhibition by dacomitinib in RLM and HLM are illustrated by the Lineweaver–Burk plot shown in Figure 6. The IC50 values and inhibitory effects of dacomitinib on poziotinib metabolism are shown in Table 3. The IC50 values of M1 in RLM, HLM and CYP3A4 were 11.36, 30.49 and 19.57 μM, respectively. The IC50 values of M2 in RLM, HLM and CYP2D6 were 43.69, 0.34 and 0.11 μM, respectively. The Ki, and αKi values of M1 in RLM are 8.18, and 38.81 μM, respectively. The Ki, and αKi values of M2 in RLM are 47.48, and 38.07 μM, respectively. These results indicated that dacomitinib was a mixed inhibitor of poziotinib in RLM and HLM. Moreover, the inhibitory effect was different for all enzymes, especially CYP2D6.

Discussion

The purpose of this research was to demonstrate alterations in the pharmacokinetics of poziotinib after the administration of dacomitinib in rats. The results indicated that this method could be used for the analysis of poziotinib in rats and in rat liver microsome samples, which could meet the European Medicines...
Figure 4. Michaelis–Menten kinetics of poziotinib in RLM (A) and HLM (B).

Figure 5. Poziotinib with various concentrations to determine the IC50 for the activity of RLM (A, B), HLM (C, D), CYP3A4 (E) and CYP2D6 (F).
After oral administration, poziotinib was slowly absorbed by plasma and reached a maximum concentration at 6 h in rats. Poziotinib was quickly eliminated from plasma with an elimination $t_{1/2}$ of 4.53 ± 0.85 h. Currently, pharmacokinetic studies of poziotinib in rats are lacking. Although Kim et al. (2013) studied the plasma concentration-time curves of poziotinib in dogs after an oral dose of 0.3 mg/kg poziotinib, the $T_{\text{max}}$ and $t_{1/2}$ values of poziotinib were 0.40–1.00 h and 3.40–5.40 h, respectively. In conclusion, the pharmacokinetic parameters of poziotinib in dogs and rats were significantly different.

The interaction between drugs is generally determined according to pharmacokinetic properties, and it occurs in the phase of absorption, distribution, metabolism or excretion (Kim TH et al. 2017; Qin et al. 2017; Darbalaei et al. 2018). Drug–drug interactions, which can produce irrelevant, synergistic, additive, and antagonistic results, are increasingly recognized as important clinical events. When rats were pre-treated with dacomitinib, the extent of absorption of poziotinib was significantly increased, and its performance was determined by the AUC$_{(0-\infty)}$, which ranged from 12597.80 ± 1994.45 µg/L/h to 22212.70 ± 2217.34 µg/L/h. In parallel, the $T_{\text{max}}$ value of poziotinib was delayed by nearly 3 h after pre-treatment with dacomitinib. Compared to control rats, the pharmacokinetic parameters in metabolism ($t_{1/2}$) were significantly increased in rats that were pre-treated with dacomitinib. These data indicate that the pharmacokinetics of poziotinib are significantly affected by dacomitinib in rats. We performed in vitro experiments to further evaluate the effect of dacomitinib on the pharmacokinetics of poziotinib metabolites. Cheong et al. (2017) predicted drug interactions between rivaroxaban and antiarrhythmic drugs in vivo and in vitro by applying Static Modelling. In this study, we measured the peak area ratios of two major metabolites of poziotinib using the same method and finally obtained the IC$_{50}$ values of M1 and M2 by conversion. According to the IC$_{50}$ values of M1 and M2, it can indicate that dacomitinib mainly inhibited the metabolism of poziotinib by inhibiting the metabolism of the CYP2D6 metabolic enzyme in HLM, while it by inhibiting CYP3A4 in RLM. One reason explanation of the difference in IC$_{50}$ values between HLM and RLM is the species difference between humans and rats. Our results also show that dacomitinib not only fully inhibit CYP2D6, but also can inhibit CYP3A4. Furthermore, the Lineweaver–Burk plot suggested that the inhibition was of a mixed type, which included competitive and non-competitive inhibition ($K_i \neq \alpha K_c$). The results showed that dacomitinib has a clear inhibitory effect on poziotinib metabolism in vitro, which agrees with the in vivo results.

From the previously mentioned results, it is known that CYP3A4 and CYP2D6 participates in the metabolism of poziotinib. There might be the potential for clinically significant interactions with modulators of the CYP450 enzyme to alter plasma concentrations when coadministered, potentially leading to
enhanced adverse effects (Danton et al. 2013; Samer et al. 2013). Poziotinib is a novel antitumor drug, and changes in its plasma concentration can cause serious adverse reactions (Romero 2018). In a phase II/II study of poziotinib combined with paclitaxel and trastuzumab, Kim TY et al. (2019) evaluated the safety and tolerability of poziotinib and defined the maximum tolerated dose (MTDs) of poziotinib as 8 mg/day. In a phase I study of poziotinib in patients with advanced solid tumours, Kim et al. (2018) proposed that the MTDs of poziotinib in the continuous or intermittent dosing schedule were 18 or 24 mg/day, respectively. Although the main adverse reactions of poziotinib were diarrhea, rash, stomatitis and pruritus in their experiments. No obvious adverse effects were observed in our study, the different findings could be due to the differences in metabolic enzymes and the physiological conditions between rats and human (Martignoni et al. 2006). The pharmacokinetics of poziotinib was significantly change by dacomitinib in rats, it provided a reference for the clinical when they are co-administered.

Conclusions
The data from this study clearly illustrate the pharmacokinetics of poziotinib and the role that dacomitinib plays in the pharmacokinetic change of poziotinib. When orally administered, dacomitinib could increase the AUC, prolong the t1/2, and decrease the CL of poziotinib. Our results also indicate that the inhibition of poziotinib metabolism by dacomitinib may be of mixed type. Consequently, since dacomitinib has an inhibitory effect on CYP2D6, an inhibitory effect on poziotinib was observed. The results of this experiment were based on rat models. Given the differences in metabolic enzymes and the physiological conditions between species, further human studies are needed.

Author contributions
Quan Zhou, Weiping Ji, Changxiong Wang and Bo Wang conceived and designed the experiments; Bo Wang, Feifei Chen, Jiqian Shen, Quan Zhou and Deru Meng performed the experiments; Quan Zhou, Jiqian Shen and Feifei Chen analysed the data; Shuanghu Wang, and Yunfang Zhou contributed reagents/materials/analysis tools; and Bo Wang, Jiqian Shen and Shuanghu Wang wrote the paper. All the authors read and approved the final manuscript.

Disclosure statement
None of the authors have any conflicts of interest related to this paper.

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