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Research Article

Effect of Fluconazole on the Pharmacokinetics of Pyrotinib Maleate: A Single-Center, Open, Single-Dose, Self-Controlled Study in Healthy Chinese Participants

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What Is Known and Objective. Pyrotinib maleate, also known as pyrotinib, is an irreversible dual receptor tyrosine kinase inhibitor that primarily targets the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). Cytochrome P450 3A4 (CYP3A4) enzyme mainly catalyzes pyrotinib, and its metabolism is influenced apparently by CYP3A4 strong inhibitor, but the effect of CYP3A4 moderate inhibitor is still unclear as a moderate inhibitor of CYP3A4 enzyme. This study evaluated the effect of fluconazole, a widespread antifungal medication, on the pharmacokinetics and safety tolerance of pyrotinib. *Methods*. This study was an open, single-dose, and self-controlled clinical trial. Eighteen healthy Chinese participants were enrolled in this study. All participants were administered fluconazole on days 6–18 and pyrotinib on days 1 and 9. The maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration–time curve from time 0 to the last measurable concentration (AUC_{0-t}), area under the concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), terminal elimination half-life ($t_{1/2}$), apparent volume of distribution (V_z/F), and apparent clearance (CL/*F*) were calculated using WinNonlin software (version 8.1). Safety tolerance was assessed throughout the process. *Results and Discussion*. Compared with the single administration of pyrotinib, the exposure level was enhanced significantly after the coadministration of pyrotinib and fluconazole. The geometric mean ratios (pyrotinib + fluconazole/pyrotinib alone) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 2.16, 3.6, and 3.5, respectively. The parameter of $t_{1/2}$ is 14.16 h and 24.03 h, and CL/*F* is 275.06 L/h and 78.42 L/h, for pyrotinib alone and with fluconazole. No serious adverse events were reported in this trial, and no participant withdrew from the trial because of adverse events. *What Is New and Conclusion*. The PK profile of pyrotinib, a CYP3A4 substrate, was significantly influenced by fluconazole, with increased exposure levels and prolonged $t_{1/2}$. Dosage adjustment is suggested for the clinical application of pyrotinib when coadministered with fluconazole or other CYP3A4 inhibitors/inducers.

1. What Is Known and Objective

Receptor tyrosine kinases (RTKs) are a class of transmembrane proteins involved in growth factor signaling [1], of which nearly 60 belonging to 20 families have been identified. Tyrosine kinases are expressed in normal cells and various tumor cells and are crucial to cell growth, tissue organ differentiation, and neovascularization [2]. More than 50% of proto-oncogenes and oncogene products exhibit tyrosine kinase activity, and abnormal expression of tyrosine kinase activity leads to disturbances in the regulation of cell proliferation, which in turn results in tumorigenesis [3].

Pyrotinib, an irreversible dual RTK inhibitor that primarily targets EGFR and human epidermal growth factor receptor 2 (HER2) [4], received conditional marketing approval from the National Medical Products Administration (NMPA) in 2018 under the trade name Erinib® [5]. It is used to treat HER2-positive patients with recurrent or metastatic

breast cancer who have not previously received trastuzumab or received it along with capecitabine [6]. Pyrotinib is currently in phase III clinical development for HER2-positive breast cancer, and previous studies have identified that pyrotinib is primarily metabolized by CYP3A4 [7], contributing approximately 90% to pyrotinib metabolism in vivo [8]. Additionally, pyrotinib is mainly excreted through feces (90.9%) [9]. A previous article [10], reported that pyrotinib pharmacokinetics were significantly affected by itraconazole, with increased exposure levels, decreased clearance rate (CL), and prolonged $t_{1/2}$. Meanwhile, decreased exposure levels of pyrotinib were obtained with coadministration of the strong CYP3A4 inducer rifampin [11]. These results suggest that the pharmacokinetic characteristics of pyrotinib are significantly affected by a strong CYP3A4 activity regulator. As for the moderate modulators of CYP3A4, previous research was performed in rats, and increased C_{max} and AUC_{0-t} values of pyrotinib were observed [7]. Similar results were obtained in the PBPK model prediction [8]. However, the effect of moderate modulators of CYP3A4 on pyrotinib pharmacokinetics, which is important for its clinical application, has not been reported in humans. In this study, the effects of moderate inhibitors on the pharmacokinetic properties of pyrotinib were evaluated in healthy participants to evaluate its use with CYP3A4 activity modulators in clinical practice.

2. Methods

2.1. Drugs Information. Pyrotinib maleate tablets, Specifications: 80 mg/tablet, 14 tablets/bottle/box, Batch number: 201212 KK, Jiangsu Hengrui Pharmaceutical Co., LTD; Fluconazole capsules (50 mg), Specifications: 50 mg/grain, 7 grains/cassette, Batch number: DL0750, Manufactured by Pfizer Ltd; Fluconazole Capsules (150 mg), Specifications: 150 mg/grain, 1 grain/cassette, Batch number: EG8967, Manufactured by Pfizer Ltd.

2.2. Ethics. This study was conducted at the Clinical Research Center of Central Hospital, Affiliated with Shandong First Medical University and Beijing Anzhen Hospital, Capital Medical University. The independent ethics committee of Jinan Central Hospital (Jinan, China) approved this clinical trial (registration no.: CTR20192721, http://www.chinadrugtrials.org.cn/). The trial was performed according to the ethical principles of the Declaration of Helsinki (revised in 2013) and the International Conference on Harmonization guideline E6 : Good Clinical Practice. All participants provided written informed consent before undergoing any study procedure.

2.3. Study Participants. Eighteen healthy participants aged 18–45 years with a body mass index between 18 and 28 kg/m^2 were eligible to participate in this study. Their health was confirmed based on medical history, physical examination, vital signs, 12-lead electrocardiography (ECG), and routine clinical laboratory tests. Participants who tested positive for HIV, syphilis, hepatitis B virus, or hepatitis C virus were excluded. Additionally, all participants had to have negative findings on screening for drugs (morphine, amphetamine, cocaine, benzodiazepine, and Cannabis sativa) using commercial kits. Participants who were taking any medication, food, or beverages influencing the disposition of pyrotinib, those who had a smoking history, or those who had consumed forbidden supplements within 3 months were also excluded.

2.4. Study Design and Processing. This study was designed as a single-center, open, single-dose, self-controlled clinical trial, which included 20 days of hospitalization. A brief flowchart of the trial design is presented in Figure 1.

The participants were admitted to the phase I clinical trial ward at D-1, and they fasted for at least 10 h overnight. The following morning (D1), participants had a standard meal within 30 min before dosing and then received 80 mg of pyrotinib orally. Blood samples were collected at predose (0) and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h after pyrotinib administration. Fluconazole was administered on day 6 at a dose of 400 mg and then 200 mg daily from day 7 to day 18. On D9, 80 mg pyrotinib was coadministered with fluconazole blood samples collected at predose (0) and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 168, and 240 h after administration, and safe tolerance was assessed during the entire process.

2.5. Blood Sample Collection and Processing. Approximately 4 mL of blood was collected in a tube containing heparin sodium anticoagulant and centrifuged at $2500 \times g$ for 10 min at room temperature. The plasma was collected and frozen at −60–−90°C for further analysis.

Plasma concentrations of pyrotinib were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). The concentration range of the calibrated standard curve was between 1.00 and 500 ng/mL. The lower limit of quantification (LLOQ) of pyrotinib was 1.00 ng/mL.

2.6. Safety Assessments. Safety was monitored through adverse events, physical examinations, vital signs, 12-lead ECG, and routine clinical laboratory tests. In addition, information on the AEs, including the type, number, frequency, and severity of the AEs, along with their relationship to treatment, was collected and summarized. All adverse events (AEs) were graded and graded according to the National Cancer Institute's Common Terminology Standard for Adverse Events (NCICTCAE v5.0), which was normatively encoded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.0 Medical Dictionary.

2.7. Data Analysis. The pharmacokinetic (*PK*) parameters of pyrotinib were calculated using WinNonlin software (version 8.1) in the noncompartment model (NCA), including the maximal plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration–time curve from time 0 to the last measurable concentration (AUC_{0-t}), area under the concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), terminal elimination half-life ($t_{1/2}$), apparent

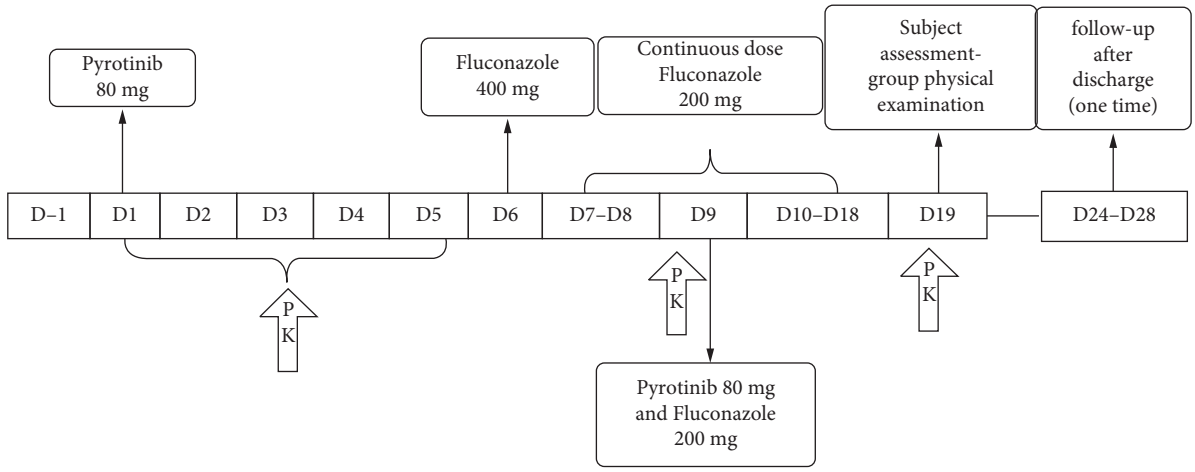

Figure 1: Study flowchart.

distribution volume (V_z/F), and apparent clearance rate (CL/F). In addition, the mean ratios and 90% confidence intervals (*CIs*) between the combination and single-dose pyrotinib were obtained using a mixed-effects model using $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} after natural logarithm transformation. When a mixed-effects model was used for analysis, the medication was used as a fixed effect, and participants participated in the model as a random effect. All statistical analyses in this study were performed using SAS software (version 9.2).

3. Results and Discussion

3.1. Demographic and Baseline Characteristics. Eighteen participants participated in the clinical trial, with fourteen participants being males and four participants being females. Due to personal reasons, subject S019 withdrew from the trial and did not complete the dose stages of fluconazole D10. In the end, only seventeen participants completed the study. Participants' demographics, including age, height, weight, and body mass index, are listed in Table 1.

Table 1: Demographic and baseline characteristics of enrolled participants ($N = 18$).

Characteristics	Mean ± SD (range)
Age (years)	33.00 ± 5.390 (23–43)
Height (cm)	168.06 ± 9.253 (150.5–179.0)
Body weight (kg)	67.45 ± 9.375 (51.3–84.0)
BMI (kg/m^2)	23.85 ± 2.372 (20.1–27.6)

BMI, body mass index.

3.2. Pharmacokinetic Results. Figure 2 shows the mean blood concentration-time profiles of pyrotinib, and Table 2 shows the relevant PK parameters. Statistical analyses of the main pharmacokinetic parameters are shown in Table 3. Due to incomplete blood sampling (the last available non-BLQ sample at a 24-hour time point) in subject S019 during the pyrotinib combined with fluconazole coadministration phase, the corresponding AUC_{0-t} and $AUC_{0-\infty}$ cannot be calculated; thus, these individual parameter values were not included in the combination phase summary and in the mixed effect model analysis. For this subject, only directly observed T_{max} and C_{max} values were included in the analyses.

At 72 hours after the drug administration during the single dosing phase of pyrotinib, only 2 subjects had detectable blood drug concentrations, and the remaining 16 subjects had their blood drug concentrations below the LLOQ of the assay. At the 96-hour time point, the blood drug concentrations in all 18 subjects were below the LLOQ. During the coadministration of fluconazole and pyrotinib, 16 of the 17 subjects (1 subject withdrew from the study) had detectable blood drug concentrations at 96 hours after the drug administration, and the blood drug concentration in 1 subject was below the LLOQ. At 168-and 240-hour time points, the blood drug concentrations in all 17 subjects were below the LLOQ.

Plasma concentration analysis showed that after oral administration of the drug, the absorption rate of pyrotinib was not significantly affected by fluconazole, with T_{max} in both groups ranging from 2–8 h. Although there was no significant difference, fluconazole significantly inhibited the metabolic process of pyrotinib in vivo. After co-administration, the in vivo exposure increased significantly, with C_{max}, AUC_{0-t}, and AUC_{inf} increasing 2.16-fold, 3.6-fold, and 3.5-fold, respectively, and the in vivo elimination rate constant related to the terminal stage of pyrotinib decreasing significantly, leading to a significant prolongation of the drug half-life. These results indicate that fluconazole significantly inhibits the metabolic excretion of pyrotinib.

3.3. Safety Assessment. In this study, pyrotinib was well tolerated by all groups. However, six AEs were reported in five participants during the study; these AEs could be related to pyrotinib. Associated AEs included nervous system, metabolic, and nutritional diseases; musculoskeletal and connective tissue diseases; and skin and subcutaneous tissue diseases. As expected, all treatment-emergent AEs were mild and likely related to the pyrotinib treatment mechanism. During the post study period, all participants who developed AEs were followed up until full recovery was confirmed.

Table 2: Summary of plasma pharmacokinetic parameters by treatment.

PK parameter (unit)	Mean ± SD (CV%)	
	Pyrotinib ($N = 17$)	Pyrotinib + fluconazole
C_{max} (ng/mL)	20.45 ± 1.30 (26.52%)	44.46 ± 1.29 (25.72%) ($N = 18$)
AUC_{0-t} (h·ng/mL)	269.60 ± 1.34 (29.82%)	980.30 ± 1.27 (24.17%) ($N = 17$)
$AUC_{0-\infty}$ (h·ng/mL)	300.60 ± 1.31 (27.36%)	1047.20 ± 1.27 (24.59%) ($N = 17$)
T_{max} (h)	5.00 (2.00–8.00)	5.00 (2.00–8.00) ($N = 18$)
t (h)	13.87 ± 1.25 (22.14%)	23.66 ± 1.20 (18.51%) ($N = 17$)
CL/F (L/h)	266.11 ± 1.31 (27.34%)	76.40 ± 1.27 (24.57%) ($N = 17$)
V_z/F (L)	5324.20 ± 1.29 (25.90%)	2606.60 ± 1.28 (24.93%) ($N = 17$)
λ_z (1/h)	0.05 ± 1.24 (22.14%)	0.03 ± 1.20 (18.51%) ($N = 17$)

PK, pharmacokinetic; C_{max}, maximum observed plasma concentration; AUC_{0-t}, the area under the concentration-time curve from time 0 to time t; $AUC_{0-\infty}$, the area under the concentration-time curve from time 0 to infinity; T_{max}, time to C_{max}; CL/F, apparent clearance; $t_{1/2}$, terminal elimination half-life; V_z/F, apparent volume of distribution; λ_z, elimination rate constant.

Table 3: Statistical analysis of pharmacokinetic parameters of pyrotinib when administered alone or with fluconazole.

PK parameter (unit)	Geometric mean		GMR*	90% CI
	Pyrotinib ($N = 17$)	Pyrotinib + fluconazole	—	—
C_{max} (ng/mL)	20.59	44.46 ($N = 18$)	2.16	(1.956, 2.385)
AUC_{0-t} (h·ng/mL)	269.6	980.3 ($N = 17$)	3.6	(3.26, 4.06)
$AUC_{0-\infty}$ (h·ng/mL)	300.6	1047.2 ($N = 17$)	3.5	(3.16, 3.84)

The effect of fluconazole on the PK of pyrotinib was assessed using the mixed model based on natural logarithm (ln)-transformed pharmacokinetic parameters. *GMR = (pyrotinib + fluconazole)/pyrotinib.

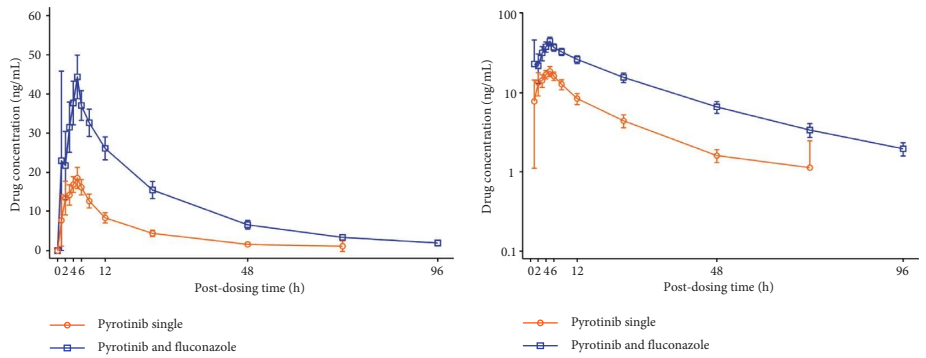

Figure 2: Linear (a) and semilogarithmic (b) scale of the mean concentration-time profiles of single-dose pyrotinib ($N = 17$) and the combination of fluconazole and pyrotinib ($N = 18$).

Two adverse events occurred in the single dosing phase of pyrotinib (D1), hypertriglyceridemia, and back pain, no adverse events were observed in the multiple dosing phases of fluconazole (D6-D8), and four adverse events occurred in the dosing phase of fluconazole combined with pyrotinib (D9-D18), including headache, dizziness, urine ketone body positive, and rash. No significant adverse events, including those leading to withdrawal from the trial or death, were reported in this study. A summary of treatment-emergent adverse events to pyrotinib is shown in Table 4.

3.4. Discussion. This study investigated the clinical interactions between pyrotinib and fluconazole. This trial of healthy participants showed that fluconazole increased pyrotinib exposure, prolonged the elimination time, and decreased clearance. However, as in previous studies [9], our study also showed that pyrotinib, along with fluconazole, is safe and well-tolerated in healthy participants.

According to the results of a phase I study on pyrotinib, the $t_{1/2}$ of a single dose of pyrotinib in healthy participants was approximately 15–20 h [12]. Therefore, the last PK blood collection point of the single-dose period of pyrotinib was set at 96 h after administration to ensure that pyrotinib was eliminated from the body before fluconazole administration. In addition, we administered an initial loading dose of fluconazole 400 mg three days prior to administering the combination of pyrotinib and fluconazole to rapidly increase the blood concentration of fluconazole to achieve high levels of CYP3A4 enzyme inhibition [13]. Fluconazole was then continued at the recommended dose of 200 mg [14].

Table 4: Summary of treatment-emergent adverse events to pyrotinib.

System organ class preferred term severity	Pyrotinib ($N = 18$)	Fluconazole ($N = 18$)	Pyrotinib + fluconazole ($N = 18$)	Total ($N = 18$)
At least one treatment-emergent adverse event	2 (11.1%)	0	4 (22.2%)	5 (27.8%)
Nervous system	0	0	2 (11.1%)	2 (11.1%)
Headache	0	0	1 (5.6%)	1 (5.6%)
Grade 1	0	0	1 (5.6%)	1 (5.6%)
Dizziness	0	0	1 (5.6%)	1 (5.6%)
Grade 1	0	0	1 (5.6%)	1 (5.6%)
Metabolic and nutritional diseases	1 (5.6%)	0	0	1 (5.6%)
Hyperlipidemia	1 (5.6%)	0	0	1 (5.6%)
Grade 2	1 (5.6%)	0	0	1 (5.6%)
Various inspections	0	0	1 (5.6%)	1 (5.6%)
Urine ketones	0	0	1 (5.6%)	1 (5.6%)
Grade 1	0	0	1 (5.6%)	1 (5.6%)
Musculoskeletal and connective tissue diseases	1 (5.6%)	0	0	1 (5.6%)
Back pain	1 (5.6%)	0	0	1 (5.6%)
Grade 1	1 (5.6%)	0	0	1 (5.6%)
Diseases of the skin and subcutaneous tissue	0	0	1 (5.6%)	1 (5.6%)
Rash	0	0	1 (5.6%)	1 (5.6%)
Grade 1	0	0	1 (5.6%)	1 (5.6%)

N, number of participants who used the study medication at least once in the corresponding phase.

When fluconazole, a moderate-strength inhibitor of CYP3A4, was used concurrently with pyrotinib, a 2.6-fold increase in pyrotinib exposure was observed, as predicted by the PBPK model [8]. In another trial [10], the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of pyrotinib were 3.78-fold, 11.8-fold, and 11.4-fold higher, respectively, in the itraconazole phase than that in the monotherapy phase. According to the results of this study, the GMR of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of pyrotinib was 2.16-fold, 3.6-fold, and 3.5-fold higher than that of the single-dose period, respectively. The results showed that although fluconazole is inhibitory effect on pyrotinib was lower than that of itraconazole, it still had a significant inhibitory effect. This indicates that the fluconazole selected in this study was feasible. Previous studies have shown that diarrhea is a common adverse event during treatment with pyrotinib, with approximately 50% of patients experiencing high levels of diarrhea [15]. It is also the most common type of AE ≥ III, and grade III diarrhea occurs predominantly in the 400 mg dose group [16]. In this study, common adverse reactions to pyrotinib included hyperlipidemia, headache, dizziness, back pain, and rash, with an incidence rate of 5.6%. In addition, there were gender differences in absorption. After combining fluconazole in female and male participants, the AUC_{0-t} was 3.74-fold and 3.44-fold, and the C_{max} was 2.71-fold and 2.03-fold, respectively, compared with the single drug. However, the statistical analysis of AUC_{0-t} and C_{max} before and after taking fluconazole in both female and male participants found that p value (p) was greater than 0.05, with no significant difference. However, due to the small sample size of this study, it is not sufficient to indicate whether there is a gender absorption difference between the two drugs in male and female participants. Further research is needed on a larger sample size.

4. What Is New and Conclusion

As a CYP3A4 substrate, the metabolic excretion process of pyrotinib significantly influences the CYP3A4 moderate inhibitor fluconazole, slowing down the metabolic clearance of the drug and increasing the exposure in vivo. The C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of pyrotinib in the combination phase were 2.16, 3.6, and 3.5 times higher than those of the single dose, suggesting that reasonable dose adjustment should be considered for clinical use. Overall, the safety profile of a single dose of pyrotinib was good as that was observed for coadministration with fluconazole.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study protocol was approved by the independent ethics committee of Jinan Central Hospital (Jinan, China). All subjects provided written informed consent before undergoing any study procedures.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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