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Original Article

Effect of cabozantinib on CYP450 isoforms activity of rats

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Abstract: Cabozantinib S-malate is a vascular endothelial growth factor receptor 2, c-MET, and RET multi-targeted tyrosine kinase inhibitor that has antiangiogenic and antitumorigenic properties with potential efficacy for the treatment of several cancers. In order to investigate the effects of cabozantinib on the metabolic capacity of cytochrome P450 (CYP) enzymes, a cocktail method was employed to evaluate the activities of CYP2B1, CYP2D1, CYP1A2, CYP3A2, CYP2C11. The rats were randomly divided into cabozantinib group (Low, Medium, High) and control group. The cabozantinib group rats were given 10, 20, 30 mg/kg (Low, Medium, High) cabozantinib by continuous intragastric administration for 7 days. Five probe drugs bupropion, metroprolol, phenacetin, testosterone and tolbutamide were given to rats through intragastric administration, and the plasma concentrations were determined by UPLC-MS/MS. Statistical pharmacokinetics difference for bupropion, phenacetin and testosterone in rats were observed by comparing cabozantinib group with control group. Combined with PCR results, continuous 7 days-intragastric administration of cabozantinib inhibits the activities of CYP2B1 and CYP1A2 of rats. Enzyme inhibition by co-administered drugs and genetic variations of their expression can increase the risk of adverse reactions. Additionally, high dosage cabozantinib may cause hepatotoxicity.

Keywords: CYP450, cabozantinib, cocktail, UPLC-MS/MS, rat

Introduction

The receptor tyrosine kinase MET and the vascular endothelial growth factor (VEGF) signaling pathway are implicated in development and progression of CRPC [1]. MET expression appears to be greater in bone metastases than primary tumors and lymph node metastases [2]; the VEGF pathway promotes bone lesion development and activates MET in advanced prostate cancer [1, 3]. Cabozantinib is an oral inhibitor of receptor tyrosine kinases including the hepatocyte growth factor receptor MET, vascular endothelial growth factor receptor 2 (VEGFR2), and rearranged during transfection receptor (RET) [4]. MET, RET, and VEGFR2 play important roles in the pathogenesis of medullary thyroid cancer (MTC) [5-7], and inhibition of these targets by cabozantinib was hypothesized to provide clinical benefit for patients with this disease [8]. The drug was approved after it met its primary endpoint of progression-free survival for the treatment of metastatic medullary thyroid cancer (MTC) [9]. Currently, it is under investigation for solid tumors and hematological malignancies in over 50 clinical trials being conducted across North America, Europe, China, Australia and the Middle East [10].

The most commonly observed adverse events associated with cabozantinib from pooled single-agent studies include fatigue, diarrhea, decreased appetite, nausea, weight loss, and vomiting. Hand-foot skin reaction (HFSR), a major dose-limiting skin toxic effect of TKIs, has been reported with cabozantinib at a frequency of approximately 40% [11]. Skin rash including HFSR, xerosis, pruritus, erythema, and pigmentary changes were also reported, but other skin manifestations have not been described [12].

Cytochrome P450 (CYP) enzymes are responsible for most biotransformation steps of xenobiotics and endogenous molecules [13].

Variations of their activity by inhibition or induction can influence the pharmacokinetics and thereby the effect of drugs (of abuse). Enzyme inhibition by co-administered drugs (of abuse) and/or genetic variations of their expression can increase the risk of adverse reactions [14] or reduce the desired effect [15]. Such drug-drug interactions were described as a major reason for hospitalization or even death [16].

So far, no study on the effects of cabozantinib on the metabolic capacity of CYP enzyme was reported. Therefore, in this study, five probe drugs were employed to evaluate effect of cabozantinib on the metabolic capacity of CYP2B1, CYP2D1, CYP1A2, CYP3A2, CYP2C11. The effects of cabozantinib on rat CYP enzyme activity will be evaluated according to the pharmacokinetic parameters changes of five specific probe drugs (bupropion, metroprolol, phenacetin, testosterone and tolbutamide).

Material and methods

Chemicals

Bupropion, metroprolol, phenacetin, testosterone and tolbutamide (all >98%) and the internal standard diazepam (IS) were obtained from Sigma-Aldrich Company (St. Louis, USA). Ultrapure water was prepared by Millipore Milli-Q purification system (Bedford, USA). Methanol and acetonitrile (HPLC grade) were obtained from Merck Company (Darmstadt, Germany).

Animals

Sprague-Dawley rats (male, 220±20 g) purchased from Shanghai SLAC Laboratory Animal Co., Ltd. Animals were housed under a natural light-dark cycle conditions with controlled temperature (22°C). All thirty-two rats were housed at Laboratory Animal Research Center of Wenzhou Medical University. All experimental procedures were approved ethically by the Wenzhou Medical University Administration Committee of Experimental Animals.

Pharmacokinetics of probe drugs in cabozantinib group and control group

Thirty-two rats (220±20 g) were randomly divided into four different dosages of cabozantinib groups (Low-group, Medium-group, High-group and control group with 8 rats in each group). Cabozantinib was dissolved in corn oil as suspension at three different concentrations (10, 20, and 30 mg/mL). Three different cabozantinib groups (Low-group, Medium-group, High-group) were respectively give cabozantinib 10, 20, and 30 mg/kg one time by intragastric administration at every morning, and last for 7 days. Control group were give saline by same administration method. At 8 days morning, five probe drugs bupropion, metroprolol, phenacetin, testosterone and tolbutamid were mixed in corn oil and given to the rats of three cabozantinib groups and control group by intragastric administration at a single dosage 10 mg/kg for bupropion, metroprolol, phenacetin, testosterone, 0.1 mg/kg for tolbutamide.

Blood (0.3 mL) samples were collected into heparinized 1.5 mL polythene tubes from the tail vein at 0.0833, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h after intragastric administration of five probe drugs. 100 μL of plasma was obtained from blood sample after centrifugation at 4000 *g* for 10 min. In a 1.5 mL centrifuge tube, 200 μL of acetonitrile (containing 50 ng/mL IS) was added into 100 μL of collected plasma sample. After vortex-mixing for 1.0 min, the sample was centrifuged at 13000 *g* for 15 min. Then supernatant (2 μL) was injected into the UPLC-MS/MS system for analysis.

Concentration of plasma probe drugs versus time was analyzed by Version 3.0 Data Analysis System (Wenzhou Medical University, China).

Statistical analysis

The main pharmacokinetic parameters of the cabozantinib group and control group were analyzed by SPSS I8.0 statistical software; statistical significance was assessed by an independent sample t-test ($P<0.05$ was considered as statistically significant).

UPLC-MS/MS determination of probe drugs

The concentration of bupropion, metroprolol, phenacetin, testosterone and tolbutamid in rat plasma were simultaneously determined by a sensitive and simple UPLC-MS/MS method [17]. The compounds were analyzed by a UPLC-MS/MS with ACQUITY I-Class UPLC and a XEVO TQD triple quadrupole mass spectrometer that equipped with an electrospray ionization (ESI) interface (Waters Corp., Milford, MA, USA).

Table 1. The sequences of the primers used in polymerase chain reaction

Isoenzymes	Forward	Reverse
CYP1A2	GTCACCTCAGGGAATGCTGTG	GTTGACAATCTTCTCAGG
CYP2B1	GACAGAAGGATGAGGGAGGAA	CTCCCTCTGTCTTTCATTCTGT
CYP2C11	AAAAGCACAATCCGCAGTCT	GCATCTGGCTCCTGTCTTTC
CYP2D1	TGAGATGTCGCTTTGGGGAC	GAGGACCACACCTTGAGAGC
CYP3A2	CTTCACAAACCGGAGGCCTTTTGGT	ATCAGGGTGAGTGGCCAGTTCATAC

Data acquisition and instrument control were performed on the Masslynx 4.1 software (Waters Corp., Milford, MA, USA).

Histopathology of liver

After pharmacokinetic properties analysis, rats were deeply anesthetized with 10% chloral hydrate (i.p., 20 mg/kg). The some liver of control group and cabozantinib treated groups were rapidly isolated and immersed in freshly prepared 4% w/v formaldehyde (0.1 M phosphate buffer, pH 7.2) for 48 h, and then embedded in paraffin. Then 5 μm-thick histological sections were prepared and stained with routine HE method (hematoxylin and eosin). The morphological changes of liver were observed under light microscope.

The mRNA expression of CYP450 in rat liver

After pharmacokinetic properties analysis, rats were deeply anesthetized with 10% chloral hydrate (i.p., 20 mg/kg). The some liver of control group and cabozantinib treated groups was removed, frozen and store at 80°C.

The livers were processed for isolation of total RNA by using TRIzol reagent (Invitrogen, Calsbad, CA, USA) according to the instruction of the manufacturer. The RNA concentration was determined, and the quality of the isolated RNA was assessed using the 260/280 nm absorbance ratio (1.8-2.0 indicates a highly pure sample). RNA integrity was confirmed by running samples on 1% agarose gel. The RNA pellet was stored at -80°C until use [18, 19].

We have used 2 μL RNA in a 20 μL reaction mixture utilizing RevertAid™ M-MuLVRT (Fermentas, Hanover, MD, USA) according to the supplier's instructions. Resulting reverse transcription products were stored at -80°C until assay.

Reactions were performed in a final volume of 20 μL that contained Platinum SYBR Green qPCR SuperMix-UDG 12 μL, 2 μL cDNA, 0.6 μL each of specific oligonucleotide primer (10 μM), and 4.8 μL DEPC-treated autoclaved distilled water.

PCR was carried out using initial denaturation at 95°C for 3 min, followed by 40 cycles of denaturation at 95°C for 30 s, annealing at 58°C (CYP1A2), 55°C CYP2B1), 56°C (CYP2C11), 63°C (CYP3A2) for 30 s, extension at 72°C for 30 s and final extension at 72°C for 45 s. The sequences of the forward and reverse primers used in this experiment are summarized in **Table 1**.

Results

UPLC-MS/MS *medthod validation*

The concentration of bupropion, metroprolol, phenacetin, testosterone and tolbutamid in rat plasma were simultaneously determined by a sensitive and simple UPLC-MS/MS method. The LLOQ for each probe drug in plasma was 2 ng/mL. The RSD of the five probe drugs were less than 15%. The calibration plot of the probe drugs is in the range of 2-2000 ng/mL ($r>0.995$). The intra-day and inter-day accuracy ranged from 90% to 115%. The matrix effects were more than 82% or less than 113%. The extraction recoveries were better than 85%.

Pharmacokinetics of probe drugs

The main pharmacokinetic parameters of bupropion, metroprolol, phenacetin, testosterone and tolbutamid calculated from non-compartment model analysis were summarized in **Table 2**. The representative profiles of concentration of drugs (bupropion, metroprolol, phenacetin, testosterone and tolbutamid) vs. time were presented in **Figure 1**.

From the **Table 2**, no difference in pharmacokinetic behaviors can be observed between low, medium dosage group and control group for bupropion, no difference in pharmacokinetic behaviors can be observed between cabozantinib group and control group for metroprolol. While from the **Table 2**, the pharmacokinetic behaviors of bupropion in high dosage group compared with the control group, $AUC_{(0-t)}$

Table 2. Pharmacokinetic parameters of probe drugs from control group and cabozantinib group rats (mean ± SD, n=8)

Parameters ng/mL*h		AUC (0-t) ng/mL*h	AUC (0-∞) h	t1/2z L/h/kg	CLz/F L/kg	Vz/F ng/mL	Cmax
Bupropion (CYP2B1)	Control	47.6±24.6	62.4±28.8	1.6±1.2	197.9±98.0	469.5±407.8	24.5±10.0
	Low	65.9±39.9	72.6±44.1	1.0±0.4	213.4±190.0	261.9±153.7	40.4±32.0
	Medium	80.3±68.0	99.1±61.5	1.5±0.8	128.2±60.4	300.8±207.0	30.3±21.4
	High	139.8±39.1**	228.0±76.7**	2.7±1.9	47.8±15.1**	158.6±62.6	60.4±17.9**
Metroprolol (CYP2D1)	Control	304.8±193.6	444.1±467.2	2.2±2.3	40.7±28.6	80.3±34.0	126.1±75.5
	Low	181.4±73.6	201.2±76.7	1.3±0.4	56.1±20.9	100.1±37.8	95.6±58.2
	Medium	343.2±147.0	365.1±184.7	1.2±0.5	31.8±10.7	48.3±15.0*	167.3±66.0
	High	223.2±61.9	298.3±160.2	2.3±3.2	41.0±18.7	84.7±67.1	79.9±20.7
Phenacetin (CYP1A2)	Control	3402.2±2476.5	3407.5±2476.6	1.0±0.5	4.1±2.4	5.8±4.1	1597.8±718.2
	Low	5171.3±444.8*	5248.5±499.5*	1.9±1.4	1.9±0.2*	5.2±3.8	2682.4±658.3*
	Medium	6232.8±2735.6	6236.0±2734.4	0.8±0.6	2.2±1.9	3.6±6.3	3213.0±1492.9
	High	10601.9±3250.0**	10856.2±3332.9**	1.4±1.3	1.0±0.3**	1.9±1.9	4028.1±1641.8**
Testosterone (CYP3A2)	Control	2576.9±1339.4	3010.4±1695.2	8.7±2.8	8.4±13.3	79.4±99.6	615.8±343.4
	Low	221.5±89.8**	318.1±161.8**	16.1±13.1	47.8±44.9*	738.4±414.9**	61.4±24.1**
	Medium	100.1±60.1**	123.7±88.5**	4.7±4.0	119.7±79.4**	609.4±291.8**	31.9±13.4**
	High	95.2±40.9**	103.5±50.5**	5.8±4.0	118.8±56.6**	750.2±514.3*	30.6±8.7**
Tolbutamide (CYP2C11)	Control	13189.4±1830.5	14790.0±2562.4	7.0±1.4	0.007±0.001	0.068±0.010	1164.1±198.5
	Low	13512.4±2088.9	14995.5±2680.0	6.7±1.4	0.007±0.002	0.065±0.011	1216.2±216.2
	Medium	12156.4±2008.8	15734.5±2131.9	9.3±2.1*	0.007±0.001	0.085±0.011*	1032.2±189.1
	High	11809.3±2235.1	12840.1±2525.6	6.0±1.3	0.008±0.002	0.069±0.014	1050.1±255.4

Cabozantinib group was compared with the control group, *: P<0.05, **: P<0.01.

increased (P<0.01), CL decreased (*P*<0.01), C_{max} increased (*P*<0.01). While for phenacetin, compared with the control group, $AUC_{(0-t)}$ increased (low, P<0.05; medium, *P*>0.05 and high, *P*<0.01), CL decreased (Low, *P*<0.05; medium, *P*>0.05; high, P<0.01), C_{max} increased (low, P<0.05; medium, *P*>0.05; high, *P*<0.01). From the **Table 2**, compared with the control group, no difference in pharmacokinetic behaviors can be observed between cabozantinib group and control group for tolbutamide. While for testosterone, compared with the control group, $AUC_{(0-t)}$ decreased (P<0.01), CL increased (Low, *P*<0.01; medium, *P*<0.05; high, *P*<0.01), C_{max} decreased (*P*<0.01).

Histopathology of liver

The pathological changes of liver were shown in **Figure 2**. In low dose group, the structures of liver lobule are intact, the central veins and portal areas can be recognized clearly at low magnification. The liver cells are arranged as funicular along with central veins and connected firmly, their nucleus are round, clear and fine luster under high magnification. There is no significant difference with control group.

In middle dose group, the structures of liver lobule are also intact, and no hepatocyte swelling, cytoplasm rarefaction or inflammatory cell infiltrating observed at high magnification.

In high dose group, although there was no obvious structure change in liver lobule and the central veins, some local damaged portal areas have been observed at low magnification. At high magnification, we found the liver cell cord derangement and liver cells arranged irregularly. The regular and tight arrangements of liver cells along with central veins were disappeared, and some liver cells were apoptosis which caused cells gap increased.

The mRNA expression of CYP450 in rat liver

After 7 days-intragastric administration of cabozantinib (**Figure 3**), the levels of CYP1A2, CYP2B1 and CYP2C11 in the cabozantinib group were decreased compared with the control group (P<0.05 or P<0.01), the mRNA expression levels of CYP1A2, CYP2B1 and CYP2C11 in the cabozantinib groups were obviously lower.

After 7 days-intragastric administration of cabozantinib (**Figure 3**), the mRNA expression levels of CYP2D1 in the cabozantinib group were decreased compared with the control group (P<0.05 or P<0.01); and the levels of CYP3A2

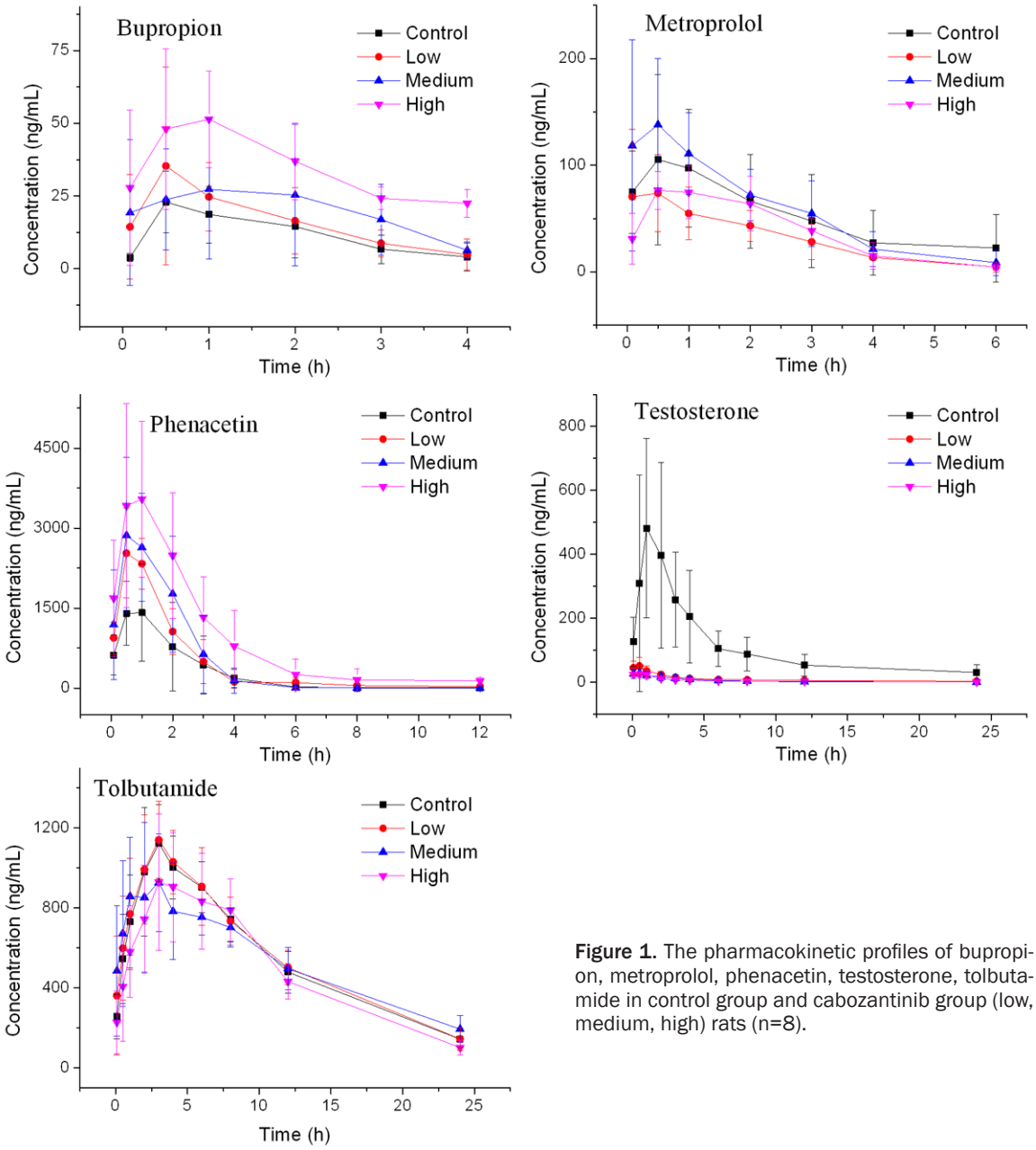

Figure 1. The pharmacokinetic profiles of bupropion, metroprolol, phenacetin, testosterone, tolbutamide in control group and cabozantinib group (low, medium, high) rats (n=8).

in the medium and high group were decreased compared with the control group ($P<0.05$ or $P<0.01$), while the levels of CYP3A2 in the low group were increased compared with the control group ($P<0.01$).

Discussion

In general, changes in pharmacokinetics are thought to be caused by drug-drug or drug-food interactions [20]. In pharmacokinetic interactions, approximately 65% of drug-drug interactions occur in metabolic sites, and drug metabolic enzymes are considered to be the most important interactive sites. A large number of drugs are metabolized by CYP enzymes in the liver, and more than 90% of drug-drug interactions occur at the CYP-catalyzed step [21, 22]. Similarly, supplement-drug interactions involving CYP activity are occasionally found to cause considerable adverse events. For these reasons, we evaluated the effects of acute cabozantinib poisoning on the activity of CYP enzymes in *vivo*. We selected CYP isoforms

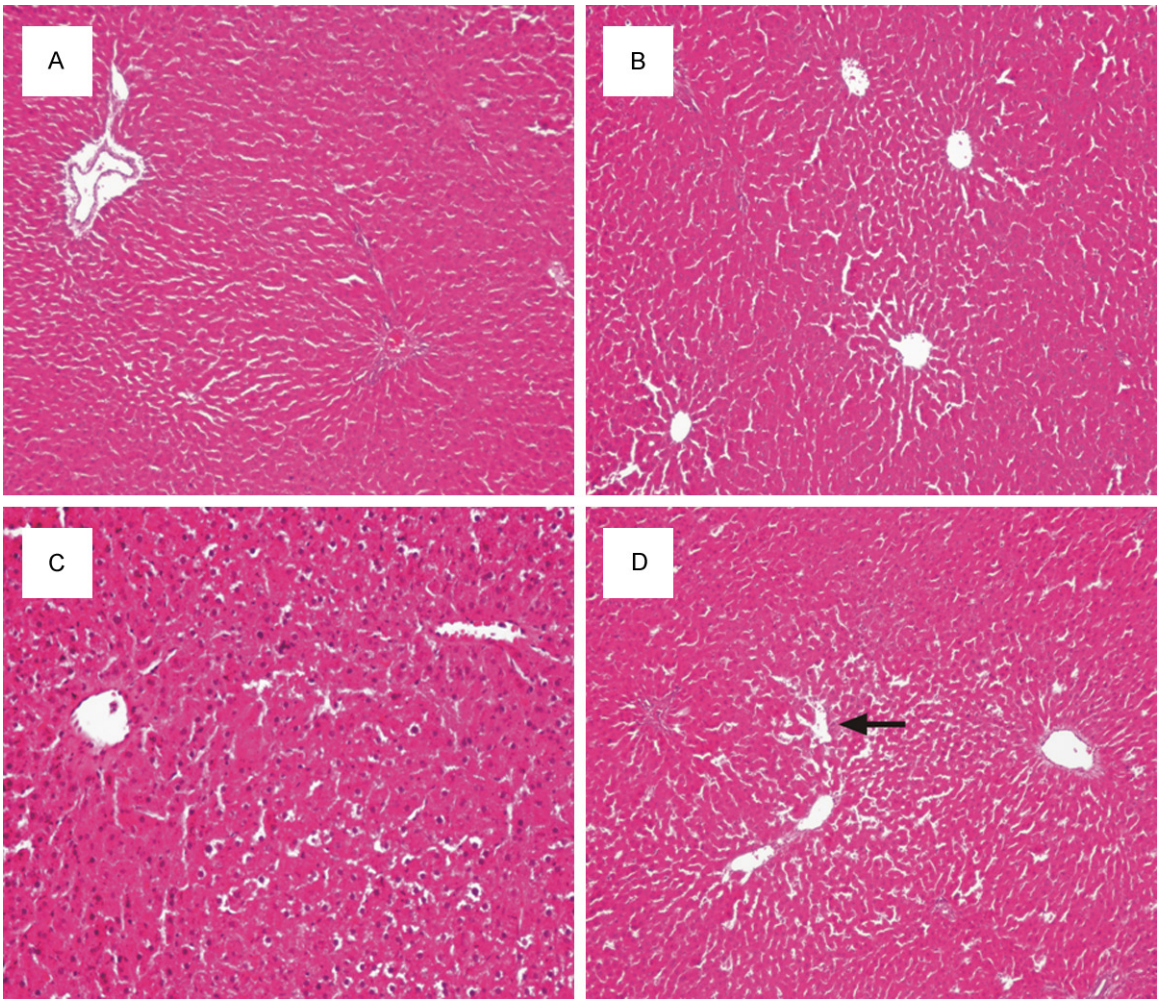

Figure 2. Morphological changes of liver in control-group (A) and low, middle, high dosage groups (B-D) (hematoxylin-eosin, ×40).

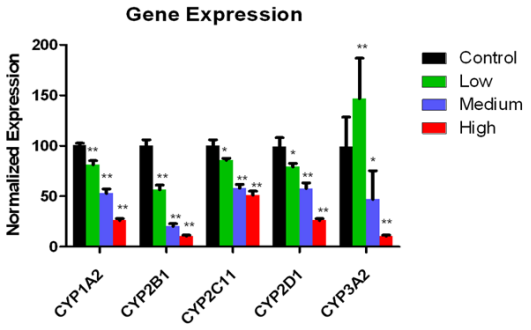

Figure 3. Effect of cabozantinib on mRNA expression of CYP1A2, CYP2B1, CYP2C11, CYP2D1 and CYP3A2 in liver of rat (n=6), *P<0.05 vs. Control; **P<0.01 vs. Control group.

CYP1A2, CYP2D1/CYP2D61, CYP3A2/CYP3A4, CYP2C11/CYP2C9 and CYP2B1/CYP2B6 because more than 90% of drugs are known to be metabolized by these 6 CYP enzymes [23, 24].

There no significant difference for AUC, CL and C_{max} of metroprolol and tolbutamide (P>0.05) between the cabozantinib group (low, medium, high) and control group was observed. It suggested that the cabozantinib was not able to induce or inhibit the activity of CYP2D1 and CYP2C11 enzyme. The pharmacokinetic parameters of bupropion and phenacetin experienced obvious change with increased $AUC_{(0-t)}$ (P< 0.05), C_{max} (P<0.05) and decreased CL (P<0.05) after the dosage increase. The mRNA expression levels of CYP2B1 and CYP1A in the cabozantinib groups were obviously lower. This result indicates that the 7 days-intragastric administration of cabozantinib could inhibit the metabolism of bupropion (CYP2B1) and phen-

acetin (CYP1A2) in rat. The pharmacokinetic parameters of and testosterone experienced obvious change after the dosage increase. However, the mRNA expression results were not consistent with the pharmacokinetic results. It indicates that the 7 days-intragastric administration of cabozantinib could not induce or inhibit the activity of the metabolism of testosterone (CYP3A2) in rat.

As cabozantinib is always administrated in combination with other drugs, interactions between cabozantinib and other drugs would increase the risk of either diminished efficacy or adverse effects. In our study, we found that 7 days-intragastric administration of cabozantinib inhibit the metabolism of bupropion (CYP2B1) and phenacetin (CYP1A2). Therefore, the metabolism and elimination of drugs would change if they are administrated in combination with cabozantinib.

After the pharmacokinetic profiles evaluation by cocktail method, we also investigated the hepatotoxicity of cabozantinib by observing the pathological changes of liver after cabozantinib administration. The pathological changes of liver were observed at three difference dosages with small changes in high dosage and no change in low dosage, **Figure 2**. Therefore, high dosage cabozantinib may cause hepatotoxicity. A more systematic and comprehensive study to investigate the hepatotoxicity of cabozantinib will be carried out.

In conclusion, the results observed in this study would provide us valuable information regarding the interactions of cabozantinib with other drugs. Inhibit of drug metabolizing enzyme CYP2B1 and CYP1A2 by cabozantinib would increase the plasma concentration of other drug. Enzyme inhibition by co-administered drugs and genetic variations of their expression can increase the risk of adverse reactions. Additionally, high dosage cabozantinib may cause hepatotoxicity.

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Disclosure of conflict of interest

None.

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