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Research Article

Effects of Ticagrelor on the Absorption and Metabolism of Imatinib in Rats

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Abstract

Background: Patients with acute coronary syndrome (ACS) who also have chronic myelocytic leukemia (CML) or gastrointestinal stromal tumor (GIST) may receive a concurrent therapy of imatinib and ticagrelor. The absorption and transport of both drugs are influenced by organic anion transporting polypeptides (OATPs), P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Furthermore, both are primarily metabolized by CYP3A4 enzymes. Thus, co-administration may lead to pharmacokinetic interactions. Therefore, this study aimed to investigate the effect of ticagrelor on imatinib pharmacokinetics in rats. **Methods**: A total of 30 Sprague-Dawley (SD) rats were randomly divided into three groups: a control group (imatinib 30 mg/kg), a low-dose experimental group (imatinib 30 mg/kg, ticagrelor 10 mg/kg), and a high-dose experimental group (imatinib 30 mg/kg, ticagrelor 20 mg/kg). All rats received the appropriate drugs once daily for 14 consecutive days. Venous blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on days 1 and 14, and the plasma was isolated. Pharmacokinetic parameters were calculated using DAS 2.0 software. **Results**: On day 1, no significant changes were observed in the pharmacokinetic parameters of either imatinib or any associated active metabolite, N-desmethyl imatinib. However, after 14 days, the high-dose experimental group showed a significant decrease in the area under the plasma concentration time curve for imatinib from 0 to 24 hours (area under the curve, AUC_{0-24}) and from 0 to infinity ($AUC_{0-\infty}$). Similarly, the AUC_{0-24}, $AUC_{0-\infty}$, and maximum concentration (C_{max}) of N-desmethyl imatinib were also significantly reduced in the high-dose experimental group. In contrast, administering 10 mg/kg ticagrelor did not significantly affect the pharmacokinetics of imatinib or N-desmethyl imatinib. The trough plasma concentrations (C_{min}) of both imatinib and N-desmethyl imatinib were not significantly altered in any group. **Conclusions**: Repeated administration of 20 mg/kg ticagrelor significantly inhibited imatinib absorption in rats. These results suggest that clinical symptoms and imatinib plasma concentration should be monitored when ticagrelor and imatinib are used concomitantly.

Keywords: imatinib mesylate; ticagrelor; drug interactions; organic anion transporters

1. Introduction

Ticagrelor is an antiplatelet agent widely used in patients with acute coronary syndrome (ACS). It exerts anti-inflammatory, antiplatelet activation and aggregation, vasodilatory, and cardioprotective effects through inhibition of P2Y12 receptors on platelets and the adenosine ENT-1 transporter on erythrocytes [1]. Ticagrelor has an absolute bioavailability of approximately 36% and is rapidly absorbed in the intestine [2]. It is primarily metabolized by CYP3A4 and CYP3A5 enzymes [3]. Both ticagrelor and its active metabolite are substrates of P-glycoprotein (P-gp) [3]. Notably, ticagrelor is also a potent inhibitor of several organic anion transporting polypeptides (OATPs), including OATP1B1, OATP1B3, and OATP2B1 [4,5], and has been shown to inhibit breast cancer resistance protein (BCRP) [6].

The plasma concentration and clinical efficacy of ticagrelor are significantly influenced by drug interactions affecting CYP3A4 activity [7]. For instance, potent CYP3A4 inhibitors like ketoconazole can markedly increase ticagrelor exposure, elevating bleeding risk, whereas strong inducers like rifampin accelerate its metabolism, reducing plasma levels and potentially compromising antiplatelet efficacy [8]. Moderate CYP3A4 inhibitors, such as diltiazem, can increase ticagrelor maximum concentration (C_{max}) and AUC by 69% and 174%, respectively [9]. Concomitant use of the P-gp inhibitor cyclosporine also significantly elevates ticagrelor exposure [10]. Additionally, intravenous morphine during the acute phase of ACS can delay and reduce ticagrelor absorption, potentially retarding its antiplatelet onset [11].

Imatinib is a cornerstone in the treatment of chronic myelocytic leukemia (CML) and gastrointestinal stromal tumor (GIST). As a tyrosine kinase inhibitor, it suppresses tumor cell proliferation by selectively inhibiting Bcr-Abl tyrosine kinase activity and platelet-derived growth factor receptor signaling [12–14]. Imatinib is well absorbed enterally, with an average absolute bioavailability of 98%. It is metabolized predominantly in the liver by CYP3A4 and CYP3A5, producing N-desmethyl imatinib as its main ac-

tive metabolite, which exhibits similar *in vitro* potency to the parent drug [13]. Imatinib itself can inhibit CYP3A4, CYP2C9, and CYP2D6. It is also a substrate for various drug transporters, including organic cation transporters (OCT), P-gp, BCRP [15], and OATPs.

The therapeutic efficacy and adverse effects of imatinib are closely correlated with its plasma concentrations. The B2222 clinical trial established that patients with a steady-state imatinib C_{min} above 1100 ng/mL experienced significantly better progression-free survival [16]. A study in 327 Chinese patients linked imatinib C_{min} to the incidence of orbital and limb edema, anemia, and rash [17]. Elevated imatinib plasma concentrations (>3200 ng/mL) are associated with increased risk of severe adverse effects such as edema, granulocytopenia and pleural pain [18]. N-desmethyl imatinib is the main active metabolite of imatinib, with its area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24}) being approximately 16% of the imatinib's [14]. Therefore, monitoring the plasma concentrations of both imatinib and N-desmethyl imatinib is crucial for optimizing efficacy and minimizing toxicity.

Clinical pharmacokinetic studies have demonstrated significant interactions involving imatinib. The potent CYP3A4 inducer rifampin decreased imatinib C_{max} and AUC_{0-24} by 54% and 68%, respectively, and increase its clearance by 385% [19]. Conversely, the CYP3A4 inhibitor ketoconazole increased imatinib C_{max} and AUC by 26% and 40%, respectively [20]. In a study by Tan *et al*. [21], it was found that in mice, metronidazole reduced C_{max} and AUC of imatinib by 38% and 14%, respectively, and advanced the time to peak concentration by 50%. Meanwhile, the AUC in liver, kidney, and brain tissues increased by 1.71-fold, 2.1-fold, and 2.3-fold, respectively [21]. It was hypothesized that these effects might be related to the inhibition of P-gp or other efflux transporters.

In summary, the overlapping metabolic and transport pathways of ticagrelor and imatinib-specifically involving CYP3A4, OATPs, P-gp, and BCRP-create a high potential for pharmacokinetic interactions. Furthermore, given that many patients with CML and GIST are elderly and have a high prevalence of cardiovascular comorbidities requiring antiplatelet therapy, co-administration of imatinib and ticagrelor is plausible [22]. This study therefore aimed to investigate the effects of single and multiple doses of ticagrelor on the plasma concentrations of imatinib and its metabolite, N-desmethyl imatinib, in rats, to provide preclinical data supporting the safe and effective clinical use of imatinib.

2. Materials and Methods

2.1 Reagent and Equipment

Ticagrelor tablets (Batch: 22310301, specification: 0.09 g) were purchased from Zhejiang Haizheng Pharmaceutical Co., Ltd. (Taizhou, Zhejiang, China). Imatinib mesylate capsules (Batch: DC7A3023, specification: 0.1 g) were from Qilu Pharmaceutical (Hainan) Co. Ltd. (Haikou, Hainan, China). Calibration controls imatinib mesylate (Batch: 420020-201702, purity: 99.3%), N-desmethyl imatinib (Catalog No.: C12543055, purity: 84.1%) and tenidazole (Batch: 100336-200703, purity: 99.8%) were purchased from the Chinese Institute for Food and Drug Control (Beijing, China). Heparin Sodium (Batch: F201230705, 2 mL:12,500 IU) was from Hebei Changshan Biochemical Pharmaceutical Co., Ltd. (Shijiazhuang, Hebei, China). Ultra-pure water (Watsons Distilled Water, Batch: 20230715) was purchased from Watsons Group (Guangzhou, Guangdong, China). Chromatographic pure methanol (Catalog No.: A452-4) and formic acid (Catalog No.: M185-500) were from Thermo Fisher Scientific (Waltham, USA). Isoflurane (Catalog No.: R5100) was from Shenzhen Ruiward Life Technology Co., Ltd. (Shenzhen, China). Sodium pentobarbital solution (Batch: Y2023012102) was from Shanghai Xiyao Biological Technology Co., Ltd. (Xi'an, Shanxi, China). The analysis was performed on an ultra-performance liquid chromatography system coupled with a Triple Quad 4500 mass spectrometer from AB SCIEX (Framingham, MA, USA).

2.2 Animals and Handling

SD rats (age: 6–7 weeks, weight: 200 ± 20 g) were purchased from Beijing Hufukang Biotechnology Co., Ltd. (License No.: SCXK (Beijing) 2019-0008). All rats were housed in a specific pathogen-free environment, with room temperature (23 ± 2) °C, relative humidity 60%, and a 12/12-hour light/dark cycle. Standard rodent chow and water were provided *ad libitum*. All cages, water bottles, and bedding were sterilized. All experimental procedures were approved by the Animal Ethics Committee of the Fourth Hospital of Hebei Medical University (Approval No. 2023206).

2.3 Plasma Samples Collection and Detection

Thirty SD rats were randomly assigned to three groups (n = 10 per group, 5 males and 5 females). Control group: received imatinib 30 mg/kg once a day for 14 days. Low-dose experimental group: received imatinib 30 mg/kg and ticagrelor 10 mg/kg once a day for 14 days. High-dose experimental group: imatinib 30 mg/kg and ticagrelor 20 mg/kg once a day for 14 days.

Approximately 50–100 µL blood samples were collected from the orbital venous plexus of each rat at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hour post-dose on day 1 and day 14. Prior to blood collection, animals were anesthetized via inhalation of 2% isoflurane. Samples were placed in heparin tubes, centrifuged at 12,000 rpm for 10 minutes, and the resulting plasma were stored at –80 °C until analysis. Upon completion of the experimental procedures, rats were euthanized. This was performed by first inducing deep anesthesia via intraperitoneal administration of a 2% sodium pentobarbital solution at a dosage of 2 mL/kg body

Table 1. Pharmacokinetic parameters of imatinib after a single dose administration.

Parameters	Control group	Low-dose experimental group	High-dose experimental group
AUC_{0-24} (ng/mL·h)	18,740.040 ± 3437.733	20,189.274 ± 6168.274	17,905.013 ± 6055.185
$AUC_{0-\infty}$ (ng/mL·h)	18,796.765 ± 3389.531	20,260.446 ± 6192.265	18,014.306 ± 5997.448
MRT_{0-24} (h)	7.102 ± 2.254	6.289 ± 0.943	6.585 ± 1.032
$MRT_{0-\infty}$ (h)	7.104 ± 2.188	6.363 ± 0.950	6.839 ± 1.266
T_{max} (h)	4.200 ± 0.632	4.600 ± 0.966	4.400 ± 0.843
C_{max} (ng/mL)	2763.000 ± 543.978	2830.800 ± 547.535	2728.600 ± 1758.899
$t_{1/2}z$ (h)	2.416 ± 0.369	2.622 ± 0.205	2.980 ± 0.956
Vz/F (mL/kg)	0.006 ± 0.002	0.007 ± 0.007	0.011 ± 0.015

AUC, area under the plasma concentration-time curve; MRT, mean residence time; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $t_{1/2}z$, half-life; Vz/F, apparent volume of distribution.

weight, followed by cervical dislocation. Concentrations of imatinib and N-desmethyl imatinib in each sample were quantified using ultra-performance liquid chromatography coupled with a triple quadrupole mass spectrometry system (UPLC-MS/MS, Triple Quad 4500), in accordance with the established methodology [23].

2.4 Statistical Treatment

The pharmacokinetic parameters of imatinib and N-desmethyl imatinib were analyzed using DAS 2.0 software (Anhui Provincial Center for Drug Clinical Evaluation, China). Statistical analyses (independent samples *t*-tests or Mann–Whitney U tests) were conducted using IBM SPSS Statistics, version 21.0 (IBM Corporation, Armonk, NY, USA). Data are presented as mean ± standard deviation, and a *p* value of less than 0.05 was considered statistically significant.

3. Results

3.1 Pharmacokinetic Parameters of Imatinib and N-Desmethyl Imatinib After Single-Dose Administration on Day 1

No statistically significant differences were observed in any pharmacokinetic parameters (AUC_{0-24}, $AUC_{0-\infty}$, MRT_{0-24}, $MRT_{0-\infty}$, T_{max}, C_{max}, Vz/F and Clz/F) for either imatinib or its metabolite N-desmethyl imatinib between the control and the two ticagrelor co-administered groups, as Tables 1,2. The plasma concentration-time profiles are shown in Figs. 1,2.

3.2 Pharmacokinetics Parameters of Imatinib and N-Desmethyl Imatinib After Multiple-Dose Administration After 14 Days

The pharmacokinetic parameters following multiple doses are presented in Tables 3,4. For imatinib, compared to the control group, the high-dose experimental group exhibited a significant 24.8% decrease in AUC_{0-24} ($p = 0.024$), a 21.1% decrease in $AUC_{0-\infty}$ ($p = 0.019$); a 41.3% reduction in T_{max} ($p = 0.007$); and an 100.0% increase in Vz/F ($p = 0.026$). For N-desmethyl imatinib, the high-dose experimental group showed a 39.8% reduction in AUC_{0-24} ($p =$

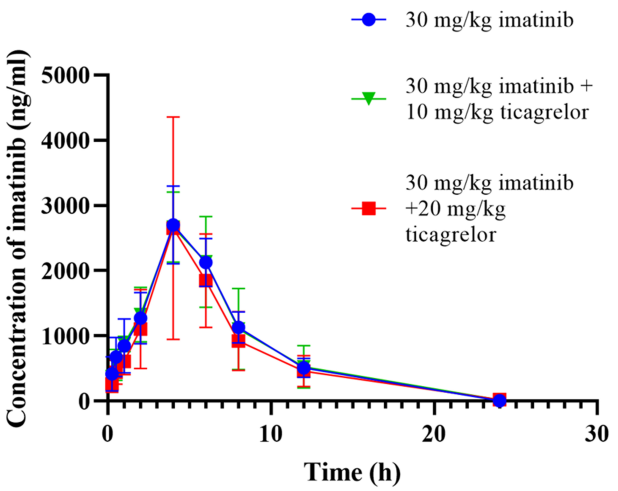

Fig. 1. Concentration of imatinib after a single dose administration.

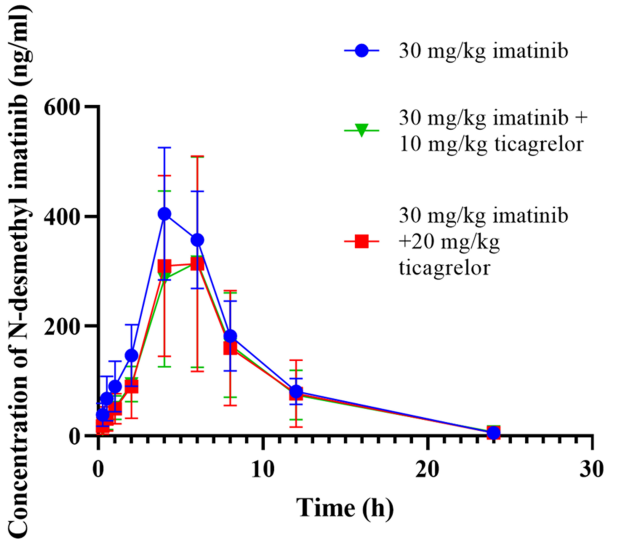

Fig. 2. Concentration of N-desmethyl imatinib after a single dose administration.

Table 2. Pharmacokinetic parameters N-desmethyl imatinib after a single dose administration.

Parameters	Control group	Low-dose experimental group	High-dose experimental group
AUC_{0-24} (ng/mL·h)	3076.796 ± 628.730	2539.390 ± 1280.753	2568.636 ± 1577.702
$AUC_{0-\infty}$ (ng/mL·h)	3113.839 ± 626.940	2564.308 ± 1292.634	2596.255 ± 1574.982
MRT_{0-24} (h)	6.841 ± 0.658	7.281 ± 0.760	7.266 ± 0.841
$MRT_{0-\infty}$ (h)	7.080 ± 0.756	7.679 ± 1.027	7.854 ± 1.291
T_{max} (h)	4.600 ± 0.966	4.800 ± 1.033	5.000 ± 1.054
C_{max} (ng/mL)	430.300 ± 113.731	380.760 ± 204.462	350.940 ± 198.492
$t_{1/2}z$ (h)	3.328 ± 0.787	3.051 ± 1.059	3.204 ± 1.181
Vz/F (mL/kg)	0.049 ± 0.017	0.053 ± 0.062	0.119 ± 0.186

AUC, area under the plasma concentration-time curve; MRT, mean residence time; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $t_{1/2}z$, half-life; Vz/F, apparent volume of distribution.

Table 3. Pharmacokinetic parameters of imatinib after multiple doses administration.

Parameters	Control group	Low-dose experimental group	High-dose experimental group
AUC_{0-24} (ng/mL·h)	72,331.633 ± 12,582.099	67,742.931 ± 18,883.973	54,368.554 ± 19,286.958*
$AUC_{0-\infty}$ (ng/mL·h)	76,993.034 ± 10,109.141	71,654.715 ± 19,624.758	60,783.863 ± 18,145.396*
T_{max} (h)	4.600 ± 1.350	3.800 ± 0.632	2.700 ± 1.160*
C_{max} (ng/mL)	6455.000 ± 1430.860	6851.800 ± 1344.155	5369.600 ± 1747.379
$t_{1/2}z$ (h)	5.544 ± 3.517	5.381 ± 0.868	8.496 ± 10.186
Vz/F (mL/kg)	0.002 ± 0.001	0.002 ± 0.001	0.004 ± 0.002*

AUC, area under the plasma concentration-time curve; MRT, mean residence time; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $t_{1/2}z$, half-life; Vz/F, apparent volume of distribution.
*$p < 0.05$, compared to the control group.

Table 4. Pharmacokinetic parameters N-demethyl imatinib after multiple doses administration.

Parameters	Control group	Low-dose experimental group	High-dose experimental group
AUC_{0-24} (ng/mL·h)	16,037.867 ± 9188.001	13,995.303 ± 4813.010	9649.778 ± 3535.576*
$AUC_{0-\infty}$ (ng/mL·h)	16,913.721 ± 9077.856	14,750.493 ± 4977.298	10,503.082 ± 3740.980*
T_{max} (h)	6.600 ± 1.647	6.000 ± 1.650	5.900 ± 1.912
C_{max} (ng/mL)	1480.600 ± 850.224	1319.900 ± 349.311	835.400 ± 309.552*
$t_{1/2}z$ (h)	5.378 ± 2.001	4.887 ± 0.812	6.018 ± 1.089
Vz/F (mL/kg)	0.010 ± 0.007	0.016 ± 0.011	0.021 ± 0.015

AUC, area under the plasma concentration-time curve; MRT, mean residence time; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $t_{1/2}z$, half-life; Vz/F, apparent volume of distribution.
*$p < 0.05$, compared to the control group.

0.023); a 37.9% reduction in $AUC_{0-\infty}$ ($p = 0.019$); and a 43.6% decrease in C_{max} ($p = 0.008$). Collectively, these data indicated that repeated co-administration of 20 mg/kg ticagrelor significantly reduced systemic exposure to both imatinib and N-desmethyl imatinib. The plasma concentration-time curves of imatinib and N-desmethyl imatinib are depicted in Figs. 3,4.

3.3 Ratio of Pharmacokinetic Parameters of N-Desmethyl Imatinib/Imatinib in Single-Dose and Multiple-Dose Administration

As Tables 5,6, the pharmacokinetic parameters of N-desmethyl imatinib/imatinib, including AUC_{0-24}, $AUC_{0-\infty}$, MRT_{0-24}, $MRT_{0-\infty}$, C_{max}, $t_{1/2}z$, showed no obvious differences between the control group and experiment groups both single- and multiple- dose administration.

3.4 C_{min} of Imatinib and N-Desmethyl Imatinib

As Table 7, C_{min} of imatinib and N-desmethyl imatinib showed no significant differences between the control group and the experiment groups after multiple doses administration.

4. Discussion

This study demonstrated that repeated co-administration of 20 mg/kg ticagrelor significantly reduced the systemic exposure (AUC_{0-24}, $AUC_{0-\infty}$) of imatinib and its active metabolite, N-desmethyl imatinib, after 14 days. Specifically, the T_{max} of imatinib was shortened, and its Vz/F increased, whereas the C_{max} of the metabolite decreased. This suggests that ticagrelor inhibits the absorption, rather than the metabolism, of imatinib. Since the impact on metabolism appears limited, key

Table 5. Pharmacokinetic parameters ratio of N-desmethyl imatinib/imatinib after a single dose administration.

Parameters	Control group	Low-dose experimental group	High-dose experimental group
AUC_{0-24} (ng/mL·h)	0.172 ± 0.064	0.136 ± 0.087	0.138 ± 0.068
$AUC_{0-\infty}$ (ng/mL·h)	0.173 ± 0.062	0.137 ± 0.087	0.139 ± 0.067
MRT_{0-24} (h)	1.013 ± 0.149	1.170 ± 0.129	1.119 ± 0.149
$MRT_{0-\infty}$ (h)	1.047 ± 0.208	1.219 ± 0.162	1.158 ± 0.110
T_{max} (h)	1.100 ± 0.211	1.050 ± 0.158	1.150 ± 0.242
C_{max} (ng/mL)	0.156 ± 0.030	0.137 ± 0.083	0.134 ± 0.053
$t_{1/2}z$ (h)	1.400 ± 0.349	1.166 ± 0.387	1.091 ± 0.323

AUC, area under the plasma concentration-time curve; MRT, mean residence time; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $t_{1/2}z$, half-life.

Table 6. Pharmacokinetic parameters ratio of N-desmethyl imatinib/imatinib after multiple doses administration.

Parameters	Control group	Low-dose experimental group	High-dose experimental group
AUC_{0-24} (ng/mL·h)	0.210 ± 0.097	0.217 ± 0.081	0.188 ± 0.049
$AUC_{0-\infty}$ (ng/mL·h)	0.210 ± 0.098	0.215 ± 0.078	0.186 ± 0.059
T_{max} (h)	1.650 ± 0.904	1.650 ± 0.474	2.300 ± 1.006
C_{max} (ng/mL)	0.215 ± 0.102	0.202 ± 0.077	0.169 ± 0.051
$t_{1/2}z$ (h)	1.068 ± 0.312	0.943 ± 0.279	1.075 ± 0.506

AUC, area under the plasma concentration-time curve; MRT, mean residence time; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $t_{1/2}z$, half-life.

Table 7. C_{min} of imatinib and N-desmethyl imatinib after multiple doses administration.

C_{min}	Control group	Low-dose experimental group	High-dose experimental group
Imatinib (ng/mL)	243.060 ± 135.030	282.800 ± 103.251	289.850 ± 139.045
N-demethyl imatinib (ng/mL)	13.634 ± 8.287	19.520 ± 5.600	17.897 ± 8.268

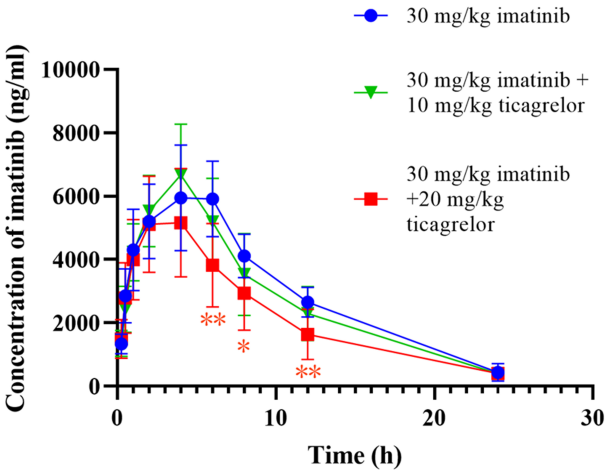

Fig. 3. Concentration of imatinib after multiple doses administration. * $p < 0.05$, ** $p < 0.01$, compared with the control group.

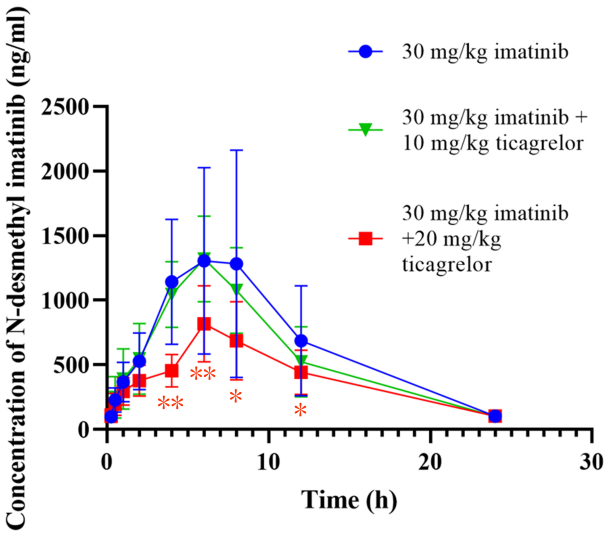

Fig. 4. Concentration of N-desmethyl imatinib after multiple doses administration. * $p < 0.05$, ** $p < 0.01$, compared with the control group.

parameters reflecting imatinib's behavior in plasma—such as T_{max}, $t_{1/2}$—were not substantially altered.

The observed changes in imatinib pharmacokinetics may be attributed to multiple potential mechanisms, with inhibition of OATPs representing a plausible primary pathway. OATPs, members of the solute carrier superfamily, are widely expressed in pharmacokinetic barrier tissues such as the gastrointestinal tract, liver, and blood-brain barrier. They facilitate cellular uptake of a broad range of drugs. OATP1B1 and OATP1B3 are predominantly localized to the sinusoidal membrane of hepatocytes and me-

diate hepatic uptake, whereas OATP2B1 is more broadly distributed, including the apical membrane of enterocytes, where it contributes to intestinal absorption [24].

Early investigations have established that ticagrelor, at clinically relevant plasma concentrations, is capable of inhibiting substrate uptake mediated by OATP1B1 and OATP1B3. Recent study have further quantified this inhibitory effect of ticagrelor on OATP1B1 and OATP1B3 [25]. A 2022 publication explicitly reported that, in a multidrug screening for OATP1B1 interactions, ticagrelor exhibited potent OATP1B1 inhibition, with a determined half-maximal inhibitory concentration (IC_{50}) value [26], confirming ticagrelor as a direct inhibitor of OATP1B1. Additionally, it has been reported that the IC_{50} of ticagrelor for OATP2B1 is approximately 2.0 μM [27].

In the present study, multiple-dose administration of ticagrelor significantly reduced the plasma exposure of both imatinib and N-desmethyl imatinib, whereas single-dose treatment showed no significant effect. The observed decrease in T_{max} and increase in Vz/F for imatinib are consistent with impaired absorption. Considering that ticagrelor is a known potent inhibitor of OATP1B1, OATP1B3, and OATP2B1, we hypothesize that it may inhibit both intestinal absorption (through competitive or non-competitive mechanisms) and subsequent hepatic uptake of imatinib, thereby reducing systemic exposure to imatinib and its metabolism to N-desmethyl imatinib.

In addition to OATP-mediated effects, the role of efflux transporters and metabolic enzymes must be considered. P-gp, an efflux transporter expressed in the intestine, liver, and kidney, limits oral bioavailability and promotes excretion of its substrates [28]. Both ticagrelor and its metabolite are substrates and weak inhibitors of P-gp [3]. Theoretically, inhibition of intestinal P-gp could enhance imatinib absorption, whereas inhibition of biliary P-gp might reduce its excretion. However, the net effect observed in this study—a reduction in imatinib exposure—suggests that any potential absorption-enhancing effect via P-gp inhibition was overshadowed by the dominant OATP-mediated reduction in absorption and hepatic uptake.

Similarly, BCRP, another efflux transporter expressed in the intestine and liver, influences drug disposition [29]. Ticagrelor is a weak inhibitor of BCRP, and imatinib is a substrate. Inhibition of BCRP might be expected to increase imatinib levels by reducing efflux; however, the observed decrease in exposure further supports the predominance of OATP inhibition.

Both ticagrelor and imatinib are substrates of CYP3A4. Ticagrelor is primarily metabolized by CYP3A4 and exhibits moderate inhibitory effects on CYP3A4 *in vitro* (IC_{50} 8–10 μM), with limited induction potential [30]. Imatinib is also mainly metabolized by CYP3A4/5. The lack of an increase in imatinib plasma concentrations—despite both drugs being CYP3A4 substrates—may be attributed to ticagrelor's relatively weak CYP3A4 inhibitory potency *in vivo*, coupled with the possibility of partial induction of alternative metabolic pathways. These CYP-mediated effects appear insufficient to counteract the pronounced reduction in imatinib availability resulting from OATP inhibition.

In this study, C_{min} of imatinib and the active metabolite N-desmethyl imatinib were not significantly reduced. Therefore, we cannot determine whether ticagrelor is able to inhibit the clinical efficacy of imatinib or attenuate adverse effects. In future studies, we will continue to investigate the effects of imatinib C_{max} and AUC with efficacy and adverse effects, and the effects of ticagrelor on imatinib through clinical monitoring of pharmacokinetic parameters and pharmacologic outcomes in patients treated with ticagrelor and imatinib. We will also investigate the molecular mechanisms by which ticagrelor inhibits imatinib absorption.

In this study, we found that high doses of ticagrelor decreased imatinib absorption and metabolism. However, such effects were not observed with low doses or single administrations. These results suggested the prolonged combination of imatinib and ticagrelor, their pharmacokinetic interaction was long-lasting and complex.

Specifically, we noted that rats in the high-dose combination group exhibited signs of increased bleeding tendency compared to the control and low-dose groups. These observations included mild nasal or oral bleeding during oral gavage administration, which was likely due to mucosal irritation from the procedure, as well as more rapid bleeding and prolonged hemostasis time during blood sampling, necessitating extended gauze compression to achieve complete hemostasis. The observed bleeding tendency at higher doses underscores the importance of dosage monitoring in clinical co-administration scenarios, particularly in patients who may already be at elevated risk of bleeding. This supports our study's objective of identifying safe and effective dosing strategies when these two agents are used together.

This study observed substantial inter-individual variability in plasma drug concentrations at each time point. Such variability likely arises from the combined effects of multiple factors, including but not limited to: (1) individual differences in the gastrointestinal absorption of the drug; (2) inherent variations in hepatic metabolic capacity and/or renal excretion function among the rats; and (3) operational deviations of several dozen seconds to one minute from the predetermined blood sampling time points. During phases of rapid drug concentration change (e.g., the absorption and distribution phases), even these minor temporal discrepancies can result in significant concentration differences. Despite this variability, the mean plasma concentration-time curve clearly delineates the fundamental pharmacokinetic profile of the drug.

This study has several limitations. First, given that this investigation was conducted in a rat model, extrapola-

tion of the results to a clinical context warrants caution owing to known interspecies differences in drug metabolism and disposition. For instance, the homology between rat OATP transporters and human SLCO1B1 is approximately 70%, highlighting a potential limitation in translating these preclinical findings directly to human applications. Consequently, further clinical data are needed to adequately assess the influence of ticagrelor on the pharmacokinetics and pharmacodynamics of imatinib in patients. Second, although a multiple-dosing regimen over 14 days was employed, it may not fully reflect the adaptive changes in enzyme induction or inhibition, or the impact on relevant transporters, that could occur during longer-term coadministration in clinical practice. Third, while we confirmed the existence of this pharmacokinetic interaction, its precise underlying mechanism remains to be elucidated through further *in vitro* studies. Finally, the sample size, while adequate for the primary endpoints, may have limited the statistical power to detect significant differences in some secondary parameters. Despite these limitations, our findings provide crucial preclinical evidence for a potential drug-drug interaction between ticagrelor and imatinib and indicate a direction for future in-depth exploration.

5. Conclusions

This study demonstrated that multiple administrations of ticagrelor inhibited the absorption of imatinib, resulting in decreased AUC of imatinib, as well as reduced C_{max} and AUC of N-desmethyl imatinib. This effect may be attributed to the potent inhibition of OATPs by ticagrelor.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization: XC. Data curation: TG, XC, NF, RF. Funding acquisition: XC. Investigation: TG, XC, NF, LD, ML. Writing–original draft, review and editing: XC, TG. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Animal Ethics Committee of the Fourth Hospital of Hebei Medical University (Approval No. 2023206) and was performed according to the animal welfare guide of U.K. Animals (Scientific Procedures) Act and preclinical experiments guide of China Food and Drug Administration.

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Conflict of Interest

The authors declare no conflict of interest.

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