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ORIGINAL RESEARCH

Development of UPLC-MS/MS Method for Studying the Pharmacokinetic Interaction Between Dasatinib and Posaconazole in Rats

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Background and Aim: Dasatinib is approved for the treatment of leukaemia worldwide. Triazole agents such as posaconazole may be used for the control of secondary fungal infection with leukaemia. This work aimed to develop a bioanalytical method to study the potential interaction between dasatinib and posaconazole.

Methods: An ultrahigh-performance liquid chromatography-tandem mass spectrometry method was established to measure the plasma concentrations of dasatinib and posaconazole in rats simultaneously. Simple protein precipitation with acetonitrile was applied to extract dasatinib and posaconazole in samples. The chromatographic separation of analytes was conducted on an UPLC BEH C18 column using a mobile phase consisting of 0.1% aqueous formic acid and acetonitrile. Dasatinib and posaconazole were monitored in positive ion mode with the following mass transition pairs: m/z 488.2→401.1 for dasatinib and m/z 701.3→683.4 for posaconazole. The method was successfully applied for pharmacokinetic interaction between dasatinib and posaconazole.

Results: The established method expressed good linearity in 1–1000 ng/mL of dasatinib and 5–5000 ng/mL of posaconazole, with limit of detection was 1 ng/mL and 5 ng/mL, respectively. Methodology validations, including accuracy, precision, matrix effect, recovery, and stability, met the US Food and Drug Administration (FDA) acceptance criteria for bioanalytical method validation. Dasatinib strongly inhibited the clearance of posaconazole in vivo, while posaconazole expressed no significant effect on the pharmacokinetics of dasatinib.

Conclusion: Dasatinib alters the pharmacokinetics of posaconazole. Attention should be paid to the unexpected risk of adverse clinical outcomes when posaconazole is co-administered with dasatinib.

Keywords: dasatinib, posaconazole, UPLC-MS/MS, interaction, pharmacokinetics

Introduction

Dasatinib is an oral tyrosine kinase inhibitor that targets the chimeric cytoplasmic protein BCR-ABL and downregulates its enzymatic activity to inhibit leukaemogenesis (Figure 1A). It is approved as first-line therapy for chronic myeloid leukaemia (CML) or as an alternative to imatinib therapy in case of intolerance or resistance.[1,2] It is also commonly used as relapse treatment in the acute phase of CML and Philadelphia chromosome-positive acute lymphoblastic leukaemia, both in adult patients and children.[3,4] Dasatinib exhibited clinical efficacy in adult patients, associated with 5-year overall survival of 18%–64%.[5] In children, the 5-year overall survival was 86% under the treatment of dasatinib.[6]

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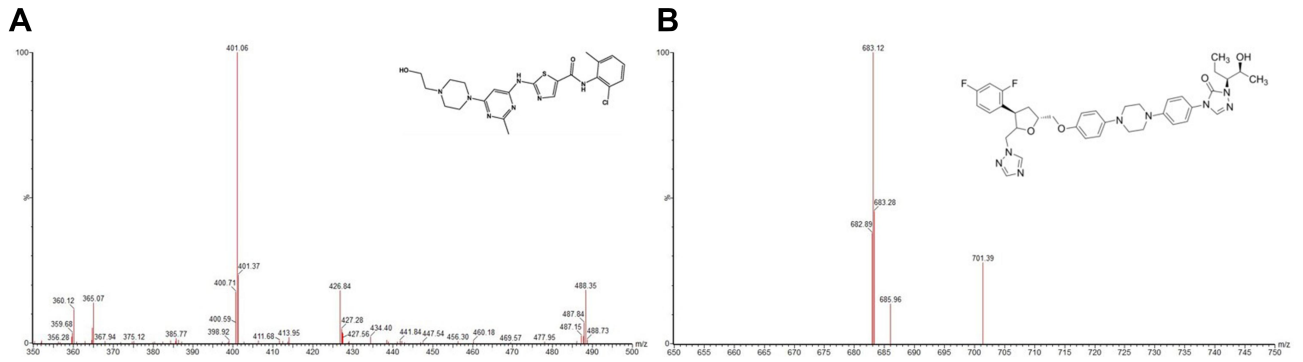

Figure 1 Mass spectra and structures of dasatinib (**A**) and posaconazole (**B**) in present study.

In the clinic, patients with acute leukaemia are considered immunocompromised and face a high risk of developing fungal infections.[7,8] Triazoles are the standard of care in patients with acute leukaemia receiving remission induction therapy or allogeneic stem cell transplantation.[9,10] Posaconazole is a second-generation triazole agent with broad-spectrum antifungal activity (Figure 1B). It is labelled for prophylaxis of invasive yeast and mold infections in high-risk immunocompromised patients with leukaemia.[11]

Dasatinib is metabolized in the liver by the CYP450 isoenzyme CYP3A4 and is subject to drug interactions with CYP3A4 inhibitors.[12,13] Ketoconazole, a classic CYP3A4 inhibitor, increases dasatinib exposure by nearly five-fold in patients, correlated with an increase in corrected QT values of approximately 6 msec.[14] It is suggested that co-administration of dasatinib with other triazoles, most of which were moderate or potent CYP3A4 inhibitors, should be avoided. By contrast, posaconazole is metabolized via UDP glucuronidation in vivo, and it is a substrate for P-glycoprotein as well.[15] The concentration of posaconazole at a steady-state was reduced by approximately 60% in a patient with a hematologic malignancy in whom posaconazole was co-administered with the UDP glucuronosyltransferase inducer carbamazepine.[16] As a substrate of UDP glucuronosyltransferase and membrane transporters,[4] dasatinib may affect posaconazole exposure. Therefore, the risk of co-administration of these two drugs should be evaluated.

There have been no reported methods for simultaneous determination of dasatinib and posaconazole to the best of our knowledge. Therefore, the objective of this study was to develop and validate a bioanalytical method based on ultrahigh-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) to measure plasma levels of these medications simultaneously and to assess potential drug-drug interaction between them in rats by comparing their pharmacokinetic profiles.

Methods and Materials

Materials and Animals

Dasatinib and posaconazole (both purities > 98%) were purchased from Canspec Scientific Instruments Co., Ltd. (Shanghai, China). Diazepam (purity > 98%) was purchased from the National Institutes for Food and Drug Control (Beijing, China) and used as an internal standard (IS). LC–MS-grade formic acid and acetonitrile were obtained from Merck KGaA (Darmstadt, Germany). Ultrapure water was prepared using a Milli-Q water purification system (Millipore Corp., Bedford, USA).

Adult male Sprague Dawley rats (267 ± 18 g) were purchased from the Laboratory Animal Centre of Wenzhou Medical University and housed at 25 °C and 40−60% relative humidity under a 12-h light-dark cycle. The rats were acclimatized for 7 days under laboratory conditions to minimize all possible sources of animal suffering prior to initiation of the experiment. All experimental animal protocols were approved by the Animal Care and Use Committee of Wenzhou Medical University and were carried out following the guidelines for the ethical review of laboratory animal welfare People's Republic of China National Standard GB/T 35892–2018.

Instrumentations and Analytical Conditions

The UPLC–MS/MS system consisted of the Waters ACQUITY UPLC I-Class system and Waters Xevo TQ-S triple quadrupole tandem mass spectrometer equipped with an electrospray ionization source (Milford, USA). All experimental data were acquired in centroid mode and

processed using MassLynx 4.1 software and the TargetLynx programme (Milford, USA).

Chromatographic analysis was performed using a BEH C18 column (2.1 × 100 mm, 1.7 μm; Waters, USA) with gradient elution. The mobile phase was made up of 0.1% aqueous formic acid and acetonitrile. The gradient programme was set as Table 1. The volume of sample injection was set at 1.0 μL. The autosampler was maintained at 10 °C, while the temperature of the column was set at 40 °C.

Analytes and IS were determined in multiple reaction monitoring modes with positive ion pairs: m/z 488.2→401.1 for dasatinib and m/z 701.3→683.4 for posaconazole; m/z 285.2→154.1 for IS. The cone voltage and collision energies were 30 V and 26 eV for dasatinib, 80 V and 30 eV for posaconazole, and 10 V and 30 eV for IS.

Preparation of the Standard Solutions

Stock solutions of dasatinib, posaconazole, and IS were dissolved to 1.0 mg/mL in methanol. The working solution was prepared by corresponding serial dilutions from the stock solution. Calibration standard and quality control (QC) samples were prepared by spiking blank plasma with appropriate volumes of the working solution. For the determination of analytes in plasma, the concentrations of calibration standards for dasatinib were set at 1, 10, 20, 100, 200, and 1000 ng/mL, and the concentrations of calibration standards for posaconazole were set at 5, 50, 100, 500, 1000, and 5000 ng/mL. The concentrations of plasma QC samples were produced at 1 ng/mL (lower limit of quantification, LLOQ), 3 ng/mL (LOQ), 500 ng/mL (MOQ), and 750 ng/mL (HOQ) for dasatinib. For posaconazole, LLOQ, LOQ, MOQ, and HOQ were set at 5, 15, 2500, 3750 ng/mL, respectively.

Table 1 Gradient Elution Programme of HPLC for Dasatinib and Posaconazole

Time	0.1% Aqueous Formic Acid (Composition, %)	Acetonitrile (Composition, %)	Flow Rate
0	90	10	0.3 mL/min
0.5	90	10	
1.0	10	90	
2.0	10	90	
2.5	90	10	
3.0	90	10	

Sample Preparation

A 100 μL aliquot of plasma sample was placed in an Eppendorf tube, and 300 μL acetonitrile containing 100 ng/mL IS was added, vortex mixed for 1 min, and centrifuged at 13,000 rpm and 4 °C for 10 min. Then the 100 μL supernatants were transferred to sample bottles, and 1-μL aliquots of the supernatant were injected for UPLC-MS /MS analysis.

Method Validation

According to the US Food and Drug Administration (FDA) guidance for bioanalytical method validation, the method validations including calibration curve, selectivity, accuracy, precision, matrix effect, recovery, and stability were performed to evaluate the method.

Pharmacokinetic Interaction Study

Twenty-four rats were randomly divided into three groups: group A (dasatinib, 10 mg/kg); group B (posaconazole, 40 mg/kg); and group C (dasatinib 10 mg/kg plus posaconazole 40 mg/kg), eight rats per group. The rats fasted for 12 h before the experiment, and only water was allowed. When the experiment was initiated, dasatinib and posaconazole dissolved in 0.1% sodium carboxymethyl cellulose (CMC-Na) orally administered to the groups A and B rats, respectively. Group C rats received dasatinib and posaconazole mixed CMC-Na solution. Blood samples were directly collected into heparin tubes via the tail vein at 0.083, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, and 72 h after administration. The plasma samples were obtained from the blood by centrifugation at 3500 rpm, 4 °C for 10 min, and 100 μL was transferred to fresh tubes. All samples were stored at −80 ◦C until use.

Statistical Analysis

The pharmacokinetic parameters were calculated using DAS software 3.0 (Bontz Inc., Beijing, China) with non-compartmental analysis. The mean concentration−time curves were constructed using GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, USA). The nonparametric Mann–Whitney *U*-test was used to evaluate pharmacokinetics' difference between dasatinib or posaconazole treatment alone group with two drugs combined treatment group by SPSS software 23.0 (IBM Corp., Chicago, USA). Pharmacokinetic profiles were expressed as mean±SD and pharmacokinetic parameters were presented as median (min-max). $P < 0.05$ represented statistical significance.

Results

Method Validation

Selectivity

The specificity of the method was evaluated by comparing the chromatograms of blank plasma from six rats with those spiked with the LLOQ of dasatinib, posaconazole, and IS. There was no interference from the endogenous substances at the dasatinib, posaconazole, and IS retention times, which were 1.67, 1.95, and 2.06 min (Figure 2), respectively.

Calibration Curve and LLOQ

A weighted ($1/x^2$) linear regression of the peak area ratio of analyte versus IS to the analyte concentration was generated to define the calibration curve. The linear relationships r^2 for the determination of two drugs in this bioanalytical assay were no less than 0.99, and the regression equations were R = 0.0734C-0.0281 for dasatinib and R = 0.0233C+0.0256 for posaconazole, where C indicates the nominal concentration level of the analyte, and R indicates the peak area ratio of analyte to the IS. The analytical signal of the analyte at the LLOQ was more than ten times of noise from the blank sample at the same retention time.

Precision and Accuracy

Six replicates of LLOQ, LOQ, MOQ, and HOQ samples were evaluated over three consecutive days to calculate the inter-day accuracy and precision. They were evaluated on the same day to calculate the intra-day accuracy and precision. A summary of the data is provided in Table 2. The intra- and inter-day accuracy of dasatinib in plasma were between -2.53% and 9.08%, and the intra- and inter-day precisions were all less than 10%. The intra- and inter-day accuracy of posaconazole in plasma were between 2.51% and 8.12%, and the intra- and inter-day precisions were all less than 11%. The precision and accuracy results met the requirements of FDA principles, ie, they should be within ±15% (±20% for LLOQ) and below 15% (20% for LLOQ), respectively.

Matrix Effect and Extraction Recovery

The matrix effect was evaluated by comparing the analyte's peak areas in the processed blank plasma samples with those of the analyte in methanol at the corresponding concentration levels. The extraction recovery was assessed by comparing the analyte chromatographic peak areas in the QC plasma samples with those of the analyte added in the processed blank plasma samples at the corresponding concentration levels. Six replicates of LOQ, MOQ, and HOQ levels were performed to assess the matrix effect and extraction recovery of dasatinib and posaconazole in plasma. A summary of the data is provided in Table 2. The matrix effect of dasatinib was calculated to range from 88.71% to 94.19%. The posaconazole was between 91.92% and 100.96%, indicating no significant ion enhancement or suppression effect from the endogenous materials in plasma during the entire assessment procedure. The average extraction recoveries of dasatinib and posaconazole in plasma were 88.88% and 80.59%, respectively.

Stability

Stabilities of dasatinib and posaconazole were assessed under various storage and processing conditions at LOQ and HOQ concentrations. As shown in Table 3, the dasatinib and posaconazole were stable in plasma at ambient temperature for 12 h, 6 h in autosampler after preparation, three freeze-thaw cycles, and 30 days at –80 °C.

Pharmacokinetic Interaction Study

The newly established UPLC–MS/MS method for concentration determination of dasatinib and posaconazole in plasma was performed to evaluate the pharmacokinetic interaction between two medications in rats. After oral administration of dasatinib alone, posaconazole alone or their combination, the mean concentrations versus time profiles in the three groups were illustrated in Figure 3. The primary pharmacokinetic parameters are listed in Table 4. When dasatinib was co-administered with posaconazole, neither the pharmacokinetic parameters nor pharmacokinetic profiles of dasatinib showed significant differences with the dasatinib alone group. However, the parameters of posaconazole in the combined treatment group, including $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, increased significantly by 8.81-fold, 9.35-fold, and 4.97-fold, respectively ($p < 0.01$). The median T_{max} of posaconazole increased from 8 h to 24 h, and $CL_{z/F}$ decreased substantially to 9.34% of the treatment alone group ($P < 0.01$).

Discussion

A method for the simultaneous determination of dasatinib and posaconazole was established. For specificity and sensitivity maximization of the two analytes, the mass spectrometric conditions were optimized. More than three product ion transitions of each analyte were

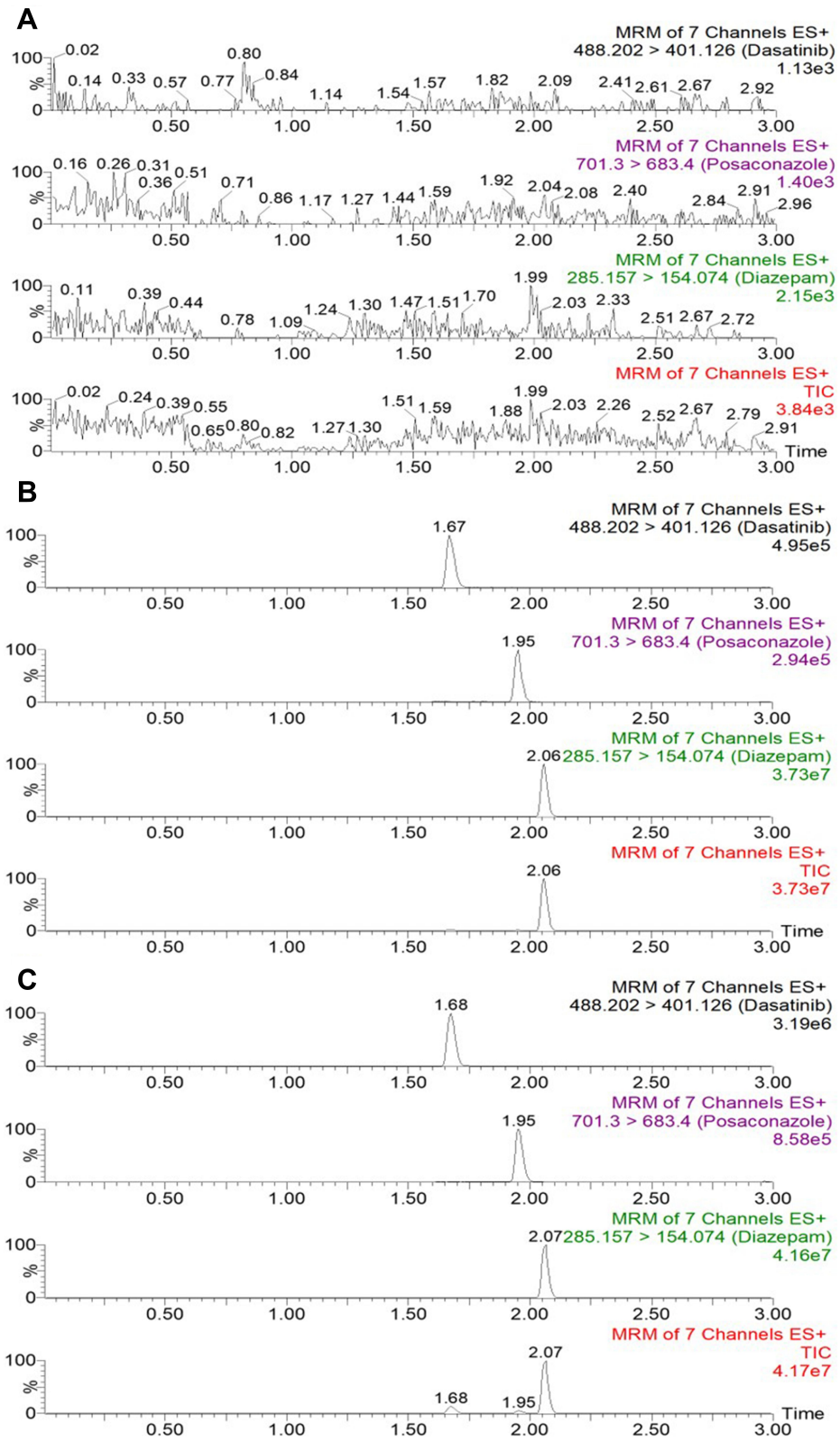

Figure 2 Representative liquid chromatograms of dasatinib, posaconazole, and IS in rat plasma sample. (**A**) blank plasma; (**B**) plasma standard of 10 ng/mL dasatinib and 50 ng/mL posaconazole; (**C**) plasma sample from combined treatment group 5 h after orally administration of dasatinib and posaconazole simultaneously.

Table 2 Accuracy, Precision, Matrix Effect and Recovery for the Analysis of Dasatinib and Posaconazole in Rat Plasma (n=6)

Analyte	Concentration (ng/mL)	Accuracy (RE, %)		Precision (RSD, %)		Matrix Effect (%)	Recovery (%)
		Intra-Day	Inter-Day	Intra-Day	Inter-Day		
Dasatinib	1	3.17	2.97	7.99	9.17	-	-
	3	5.84	−2.53	7.65	7.45	88.71±2.54	89.87±4.32
	500	9.08	6.86	2.69	3.54	94.19±6.9	87.85±2.32
	750	5.23	7.06	5.36	3.85	92.47±7.24	88.93±3.27
Posaconazole	5	7.29	4.21	6.74	10.11	-	-
	15	6.36	7.39	7.44	6.93	91.92±8.41	86.20±8.02
	2500	6.31	8.12	6.48	3.53	100.96±5.86	78.50±9.09
	3750	2.51	4.34	8.53	3.88	98.57±7.74	77.06±8.40

Table 3 The stability for the Analysis of Dasatinib and Posaconazole in Rat Plasma (n=6)

Analytes	Concentration (ng/mL)	Stability (%)			
		Ambient, 12 h	Autosampler, 6 h	Three Freeze-Thaw Cycles	−80 °C, 30 Days
Dasatinib	3	7.42	8.42	5.35	5.12
	750	6.03	3.92	4.68	5.88
Posaconazole	15	3.96	5.6	7.76	6.21
	3750	5.82	4.2	4.14	2.95

compared to produce the highest sensitivity of analytes. Furthermore, optimized cone voltage and collision energy were set for the intensity and relative abundance of precursor ions and fragment ions. Dasatinib and posaconazole were found to yield a higher response in positive mass mode than in negative mode. The most abundant fragment ions for multiple reaction monitoring were m/z 488.2→401.1 and m/z 701.3→683.4, with cone voltage values of 30 V and 80 V, collision energy values of 26 eV and 30 eV for dasatinib and posaconazole, respectively.

Several studies described the LC-MS/MS-based detection method of dasatinib in plasma.[17–19] Although these studies developed determination methods for dasatinib with high sensitivity and accuracy, liquid-liquid extraction and solid-phase extraction were chosen for sample

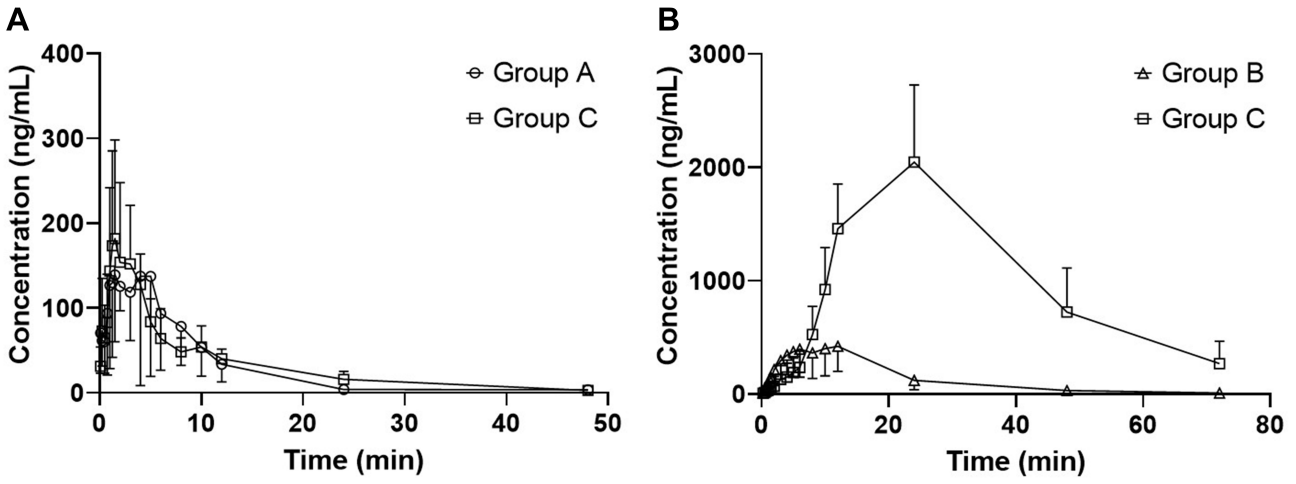

Figure 3 Mean concentration-time curves of dasatinib and posaconazole in dasatinib treatment alone group, posaconazole treatment alone group, and two drugs combined treatment group (**A** and **B**). Group A: 10 mg/kg dasatinib; group B: 40 mg/kg posaconazole; group C: 10 mg/kg dasatinib plus 40 mg/kg posaconazole. Each time-point represents the mean±SD.

Table 4 The Main Pharmacokinetic Parameters of Dasatinib and Posaconazole in Three Groups (n = 8 Each Group)

Parameters	Group A	Group B	Group C	
			Dasatinib	Posaconazole
AUC_{0-t} (ng*h/mL)	1350.86 (878.02–2376.38)	7528.97 (4217.76–17,907.69)	1395.6 (1059.6–1905.2)	73,856.23 (25,260.08–97,420.83)**
$AUC_{0-\infty}$ (ng*h/mL)	1371.08 (878.2–2376.44)	7617.16 (4533.24–18,087.2)	1677.42 (1155.2–2185.62)	78,809.65 (26,028.33–121,006.9)**
$t_{1/2z}$ (h)	4.52 (3.04–14)	12.43 (9.63–23.75)	9.63 (3.06–19.92)	15.25 (10.72–24.33)
T_{max} (h)	1.75 (1–5)	8 (4–12)	1.375 (1–3)	24 (12–24)**
$CL_{z/F}$(L/h/kg)	7.36 (4.21–11.39)	5.46 (2.21–8.82)	5.97 (4.58–8.66)	0.51 (0.33–1.54)**
C_{max} (ng/mL)	189.72 (108.48–399.19)	390.27 (204.63–892.45)	175.91 (131.62–403.32)	2329.47 (1119.42–2680.17)**

Note: **p < 0.01, significant in comparison with group A or group B.

Abbreviations: AUC_{0-t}, area under the curve from time zero to the last quantifiable concentration; $AUC_{0-\infty}$, area under the curve from time zero to infinity; $t_{1/2z}$, half-life; T_{max}, time to maximum concentration; $CL_{z/F}$ clearance; C_{max}, maximal plasma concentration.

preparation. These were expensive and required long times. Another two studies established the mass spectrometry method of posaconazole in human plasma.[16,20] Because these two methods were applied for pharmacodynamics and toxicity evaluation, the LLOQ settings were not low enough for pharmacokinetic study. Therefore, in addition to lower LLOQ, we sought to shorten the analytical time as well. To accomplish this, we used a gradient elution programme for chromatographic analysis of three analytes. Dasatinib, posaconazole, and diazepam could be separated absolutely in 3.0 min with a symmetrical peak. A rapid and straightforward plasma protein precipitation with acetonitrile was applied for sample preparation, which is suitable for subsequent experiments such as the pharmacokinetic study and met the requirements for high-throughput detection. Additionally, 0.1% formic acid was added to water to optimize the mobile phase and enhance the mass spectrometric signal intensities of analytes in this study. The LLOQs of dasatinib and posaconazole in this study was set at 1 ng/mL and 5 ng/mL, respectively.

The newly established UPLC–MS/MS method was successfully applied for concentration determination of dasatinib and posaconazole in plasma to evaluate the pharmacokinetic interaction between two medications in rats. When dasatinib was co-administered with posaconazole, neither the pharmacokinetic parameters nor pharmacokinetic profiles of dasatinib showed significant differences with the dasatinib alone group. This finding suggests that posaconazole did not affect the pharmacokinetics of dasatinib at a clinically relevant dosage. The dose of dasatinib needs not to be adjusted when administered concomitantly with posaconazole. However, the parameters of posaconazole in the combined treatment group changed significantly. This finding suggests that dasatinib expressed a significant inhibitory effect on the metabolism of posaconazole in vivo. This may due to the substrate competition caused by dasatinib. Dasatinib is a substrate of UDP glucuronosyltransferase, which is the same as posaconazole. Dasatinib may completely bind to UDP glucuronosyltransferase and cause the delayed metabolism of posaconazole in vivo. Therefore, unexpected risk of clinical outcomes may occur when posaconazole is co-administered with dasatinib, and dose adjustment should be considered in case of side effects.

Conclusions

The method established in this study to determine dasatinib and posaconazole simultaneously in rat plasma was simple, fast, and accurate. This bioanalytical method was successfully applied for the evaluation of pharmacokinetic interaction between dasatinib and posaconazole in rats. Dasatinib significantly increased the exposure to posaconazole in vivo. Therefore, the combination use of posaconazole with dasatinib should be monitored to avoid the occurrence of side effects.

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Disclosure

The authors declare no conflicts of interest.

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