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Effects of different doses glimepiride intake on the pharmacokinetics of benzbromarone in rats

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Abstract: Benzbromarone (BNR) is prescribed for the management of hyperuricemia, whereas glimepiride (GLM) for the treatment of Type 2 Diabetes Mellitus. Both drugs are certified to be mainly metabolized via cytochrome P450 (CYP) 2C9 in vivo and may have the potential drug-drug interactions. This study aims to investigate the possible influence of orally administered low- and high-dose glimepiride (GLM) on pharmacokinetic characteristics (PK) of benzbromarone (BNR) in rats. Fifteen rats were randomly assigned to group A, B and C (n=5) and administered 0.5% sodium carboxymethyl cellulose (CMC), 0.5mg/kg GLM (low-dose) and 1.0 mg/kg GLM (high-dose) once daily for 8 days, respectively, which were all followed with a single oral dose of BNR (9.0 mg/kg) on the day 8th. Blood samples were obtained from retroorbital plexus at the time points of 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24h and BNR in plasma was quantitated by HPLC-MS/MS assay. Resultantly a slight influence of GLM on PK of BNR could be found in rats. When compared with Group A, the half-life time ($t_{1/2z}$) of BNR in Group B and C significantly decreased 52.39% and 73.49%, respectively, although other major PK parameters were negligibly changed by co-administration of GLM. On the whole, the combinational therapy of GLM at low or high dose would notably alter the elimination of BNR and the effect was dose-dependent.

Keywords: Glimepiride, benzbromarone, pharmacokinetics, HPLC-MS/MS.

INTRODUCTION

Hyperuricemia and gout are well-known global health challenges, accounting for 7.44 million patients worldwide in 2017 (Mattiuzzi *et al*., 2020). The prevalence has increased dramatically in recent years. Hyperuricemia is a primary risk factor for Type 2 Diabetes Mellitus (T2DM) in gout patients (Krishnan *et al*., 2013). Previous research identified that men with gout had a 34~66% higher risk of developing T2DM than men without gout after adjustment for various factors (Choi *et al*., 2008). Hyperuricemia and T2DM are chronic metabolic diseases necessitating continuing multi-drug therapies and regular self-management in diet and exercise. Thus, co-administration of uricosuric agent and antidiabetic drug are widely used in the treatment of chronic hyperuricemia and T2DM.

Glimepiride (GLM) is currently one of the widely prescribed oral antidiabetic drug, which belongs to the third generation sulfonylurea hypoglycemic agent and stimulates the release of insulin from functioning pancreatic β cells (Moon *et al.*, 2014). Then, the peripheral tissues may improve the sensitivity to insulin under the action of GLM towards lowering blood glucose (Davies *et al*., 2018). T2DM patients received the effective treatment of GLM with the recommended dosage at the range of 1-4 mg/kg in China. GLM is completely absorbed through the gastrointestinal tract, with nearly 100% of the superior bioavailability and 5-8h half-life time ($t_{1/2}$) in humans (Yüzüak *et al.*, 2007; Rosenkranz *et al.*, 1996). GLM is principally metabolized via CYP2C9, a significant human hepatic cytochrome P450 (CYP) enzyme (Kazuko *et al.*, 2006). The pharmacokinetic (PK) interaction study had revealed that some drugs altered GLM metabolism, such as losartan and pitavastatin, while GLM did not affect the PK characteristics of losartan, teneligliptin and rosuvastatin (Chen *et al.*, 2015; Surendran *et al.*, 2017; Park *et al.*, 2019; Kim *et al.*, 2017). Simultaneously, soft drinks and liquorice juice showed significant effects on the GLM bioavailability, whereas grape juice had no influence (Hamad *et al*., 2019; Hamad *et al.*, 2007).

Benzbromarone (BNR) is a potent uricosuric drug approved for the therapeutic use of hyperuricemia and chronic gout for nearly 30 years (Yamasaki K *et al.*, 2021). Although the withdrawal of BNR was due to the reports of severe hepatotoxicity in European markets in 2003, the drug has been still available around Asia and several European countries, based on the great efficacy for

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lowering uric acid in gout patients. The $t_{1/2}$ of BNR is approximately 3h, while one primary metabolite, 6-hydroxybenzbromarone, has been reported up to 30h (Lee *et al.*, 2008). Previous researches had reported that CYP2C9 played a crucial role in the metabolism of BNR. Additionally, BNR is an inhibitor of CYP2C9. It is related to drug-drug interaction dependent on the same enzyme for clearance, such as warfarin enhancing the anticoagulant efficacy of warfarin through an enantioselective inhibition of CYP2C9-mediated metabolism *in vivo* and *in vitro* (Damkier *et al.*, 2019). To our knowledge, both drugs are metabolized by the same metabolic enzyme CYP2C9. The elimination of BNR has been shown to have significant inter-individual differences (Walter-Sack *et al.*, 1988; Walter-Sack *et al.*, 1990). However, no drug-drug interaction study had been revealed for co-administration of GLM and BNR. Thus, the goal of the current study was to observe the possible PK effects of orally administered low- and high-dose GLM on BNR in healthy male rats.

MATERIALS AND METHODS

Chemicals and reagents

GLM was purchased from the European Pharmacopoeia (Europe). BNR was obtained from J&K Scientific Ltd (Beijing, China). Tolbutamide used as the internal standard (IS) was acquired from Sigma. HPLC-MS grade acetonitrile and methanol were procured from Merck Company (Darmstadt, Germany). Other reagents were of the highest grade or analytical grade. Deionized distilled water was used throughout the experiments.

Pharmacokinetic study design

Fifteen male Sprague-Dawley rats weighing from 180 to 220g were obtained from the Experimental Animal Center of Luye Pharma (Yantai, China) and placed in a light-control environment at a temperature of 25ºC and a relative humidity of 50%. The Institutional Animal Experimentation Ethics Committee approved the animal experimental protocols of Yantai University. The rats were randomly divided into 3 groups (A, B and C). Groups A, B and C were separately administered 0.5% sodium carboxymethyl cellulose (CMC), 0.5mg/kg GLM (low-dose GLM) and 1.0mg/kg GLM (high-dose GLM) for 8 days. A single dose of BNR (9.0mg/kg) was orally provided after administration of CMC or GLM on the day 8th. The rats were fasted for 12h but permitted free access to water before the experiment. Blood samples (0.25ml) were collected from the suborbital veniplex of rats into heparinized Eppendorf tubes at predose and at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24h after BNR administration. Plasma samples were immediately centrifuged at 13,000 rpm for 5 min and stored at -80ºC till analysis.

Sample analysis

3mL ethyl acetate and 50µL IS (100 ng/mL) were added to 50µL plasma sample by vortexing for 1 min, followed by centrifugation at 12,000 rpm for 10 min. The supernatant was separated and evaporated under a gentle stream of nitrogen gas at 37ºC. The residue was reconstituted into 100µL mobile phase by vortex mixing for 20s. A total of 50µL of the supernatant was transferred to flat bottom insert and then 5µL was injected. The concentrations of BNR were determined by using a validated HPLC-MS/MS method.

HPLC-MS/MS analysis

Plasma BNR concentrations were determined by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). IS (50µL) was added to plasma, then extracted using ethyl acetate (3mL). Chromatographic separation was performed in Agilent 1100 series HPLC system using the Shim-pack XR-ODS C18 column (50 × 2.1mm, 2.2µm), with mobile phase (acetonitril/0.1% formic acid, 80/20, v/v) delivered at a flow rate of 0.3 mL/min and 30ºC column temperature. Electrospray ionizaiton (ESI) source with negative ionization mode at the following selective reaction monitoring (SRM) transition: *m/z* 422.8→250.6 for BNR, *m/z* 269.0→170.0 for IS. After optimization, the source parameters were set as follows: ion spray voltage, 3.0 kV; capillary temperature, 350ºC; sheath gas presssure, 30 psi; auxiliary gas pressure, 5 psi; collision energy voltage of BNR and IS, 37 and 18eV respectively. The dwell time was set at 100ms with each SRM transition. Data acquisition and evaluation were performed by the Xcalibur workstation (version 1.4.1). The product ion spectra of BNR (A) and IS (B) were presented in fig. 1.

Preparation standard solutions, quality control (QC) and IS

Stock solutions of BNR and IS were prepared in methanol at concentration of 0.1mg/mL and 1.0mg/mL. Working standard solutions of BNR were appropriately diluted with methanol ranging from 5 to 5000ng/mL. The concentration of the calibration standards were 5, 25, 100, 250, 500, 1000, 2500, 5000 ng/mL for BNR. Then, 100µL of each BNR standard solution was spiked into 50µL blank plasma and 50µL IS solution and extracted with ethyl acetate in a 50-mL Eppendorf tube. The processed samples were subjected to HPLC-MS/MS. The same procedure was followed to prepare three plasma QC samples at 100, 500 and 2500 ng/mL for BNR, which were separately treated as the low, medium and high QC samples. The stock solution of IS was prepared and diluted in methanol to acquire working standard solution (100 ng/mL). All extracted samples were stored and evaluated at 4ºC for 24h.

STATISTICAL ANALYSIS

Plasma level-time profiles of BNR were assembled by drawing a curve between average plasma levels and time. The PK parameters of BNR were calculated by non-compartmental analysis using DSA software (version 3.0, Bontz Inc., Beijing, China).

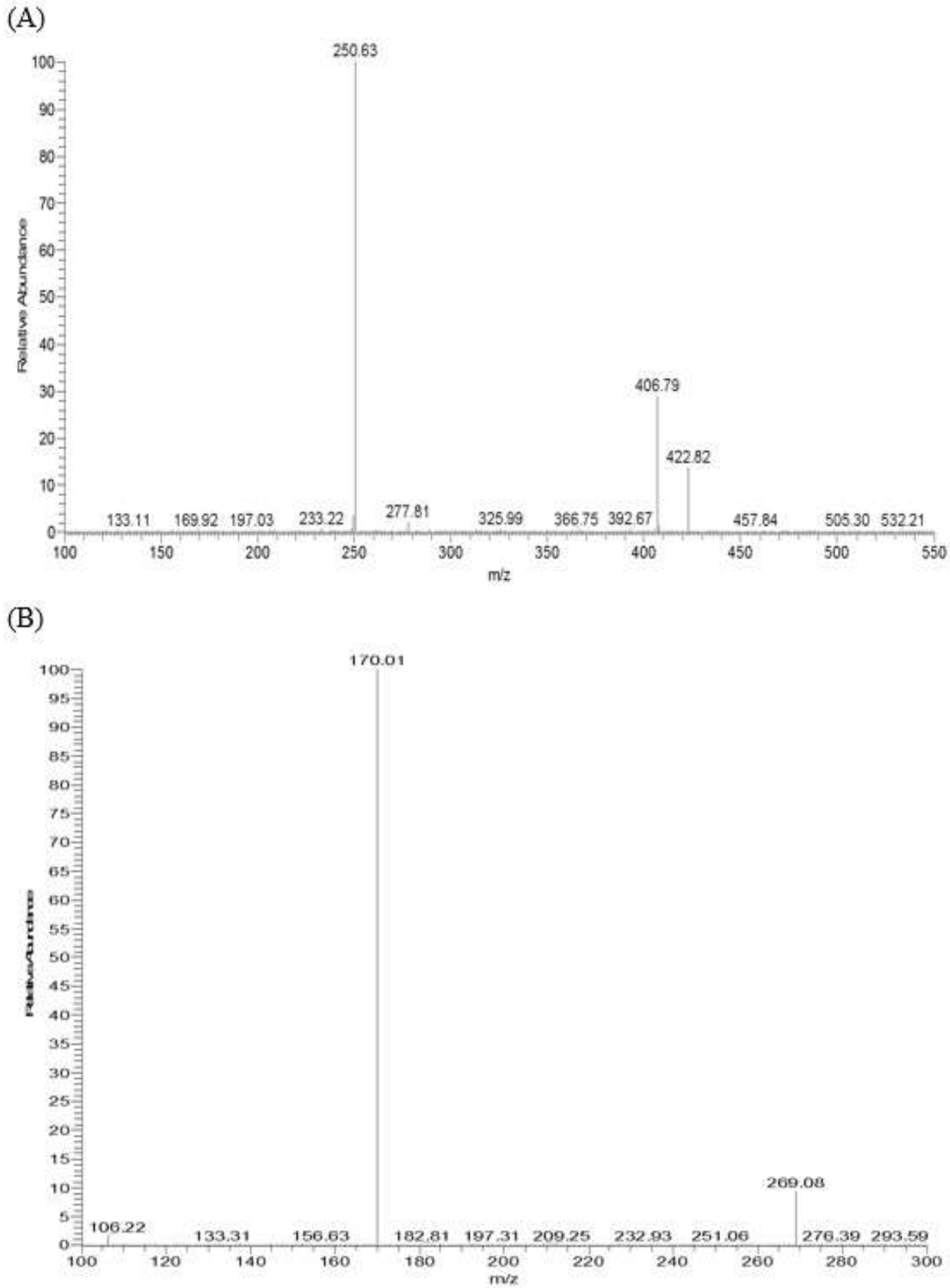

Fig. 1: Production spectrum of BNR (A) and IS (B).

Non-parametric rank-sum test was used for the statistical test of $t_{1/2z}$, one-way analysis of variance (ANOVA) was carried out to identify significant tests of the remaining PK parameters, which included $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, T_{max}, C_{max} and CL. The statistical analysis was applied by SPSS 25.0 (International Business Machines Corporation, New York, USA) software, and $p<0.05$ was considered to be statistically significant. The experimental results were represented as mean ± standard deviation (mean ± SD).

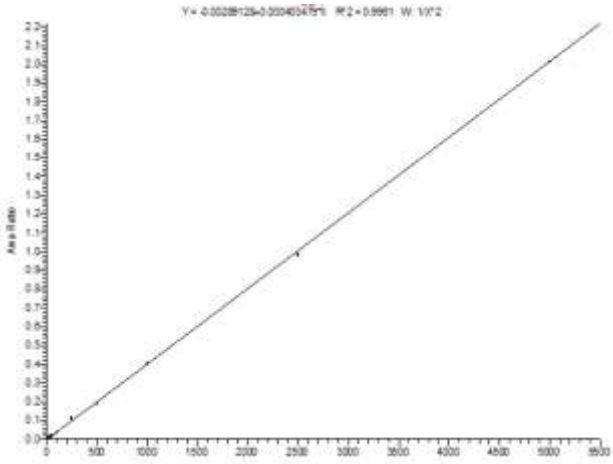

Fig. 2: The standard curve and regression equation of BNR.

RESULTS

Method validation

The HPLC-MS/MS chromatograms of blank plasma spiked with BNR and IS with reasonable peak time of 2.52, 1.06 min, respectively. The compounds separated well and were not disturbed by other endogenous substances, indicating that this method was specific.

The linearity of each calibration curve was determined by plotting the peak area ratio (Y) of BNR to IS versus the nominal concentration (X) of BNR with the weighing factor of $1/X^2$ least-square linear regression in fig. 2. The regression equation was calculated as Y=0.0004035 X+0.0028913 (r=0.9980) for BNR within a 5~5000 ng/mL linear range. Furthermore, the lower limits of quantification (LLOQ) were calculated based on a signal-to-noise ratio of 10, confirming that this method was sensitive for the quantitative evaluation of BNR, so the LLOQ value was 5.0ng/mL for the compound.

The intra-day and inter-day precision of BNR was less than 15%. The matrix effect ranged from 95.7% to 101.8%. The recoveries were above 85.0%. The stability of BNR in variation condition (room temperature for 6h, auto-sampler temperature for 24h, 3 freeze-thaw cycles, -20°C for 30 days) was acceptable, the accuracy was within 86% and 110%, and precision was less than 15%.

Benzbromarone concentrations

As presented in fig. 3, BNR concentrations were not obviously lower or higher after concomitant administration with different doses for GLM management. The maximum serum concentrations were appearing earlier and extremely approaching after 1h in the experimental groups (Group B, Group C), but the Group A ones needed at least 2h.

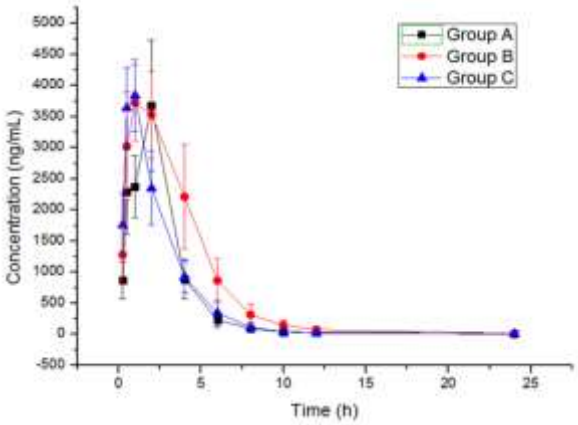

Fig. 3: Plasma concentration-time profiles of BNR after oral administration of 9.0 mg/kg BNR to rats. (A, 0.5% CMC; B, 0.5 mg/kg GLM; C, 1.0 mg/kg GLM; D, 3 groups)

PK parameters of BNR

In addition, the main PK parameters of BNR administered alone (Group A) or in combination with low and high doses GLM (Group B: 0.5mg/kg GLM, Group C: 1.0 mg/kg GLM) were illustrated in table 1. When co-administered with different doses GLM, only the elimination half-life time ($t_{1/2z}$) of BNR was drastically decreased for both B and C groups ($p<0.05$), while other pharmacokinetic parameters had no statistically significance (fig. 2, table 1). When compared with $t_{1/2z}$ in Group A, the significant value $t_{1/2z}$ of BNR was separately reduced by 52.93% for Group B and 73.49% for Group C ($p<0.05$). Although the $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and T_{max} values of BNR with administration low-dose GLM were increased by 53.74%, 52.87% and 23.53%, these changes were not meaningful from the statistical point of view in group B. Meanwhile, the CLz/F was decreased by 34.40% and the C_{max} was changed slightly. The T_{max} was lowered 47.06% and other parameters were altered unnoticeably in group C, such as $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max}. When compared with $t_{1/2z}$ in Group B, the $t_{1/2z}$ of BNR was also clearly reduced by 52.93% in group C ($p<0.05$). It was not significant for the other parameters ($p>0.05$), such as $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and T_{max} of BNR were decreased by 35.11%, 35.22% and 44.31%, separately, while the CLz/F was raised by 54.49% and the C_{max} was hardly changed. The results illustrated that GLM only slightly influenced the metabolism rate of BNR after two different doses treatment.

Table 1: The main pharmacokinetic parameters of BNR in three groups (n=5)

Parameters	Unit	Group A	Group B	Group C
$AUC_{(0-t)}$	μg/L·h	11218.073±1624.918	17246.456±2685.804	11190.486±2042.337
$AUC_{(0-\infty)}$	μg/L·h	11305.111±1671.325	17281.942±2702.683	11195.36±2037.529
$t_{1/2z}$	h	5.869±3.916	2.794±1.141*	1.556±0.346*#
T_{max}	h	1.7±0.671	2.1±1.245	0.9±0.224
CLz/F	L/h/kg	0.814±0.149	0.534±0.104	0.825±0.142
C_{max}	μg/L	3980.364±443.154	3925.154±548.37	3954.668±451.712

Notes: * P<0.05 in comparison with Group A; # P<0.05 in comparison with Group B. Group A, 0.5% CMC; Group B, 0.5 mg/kg GLM; Group C, 1.0 mg/kg GLM.

DISCUSSION

GLM and BNR are widely used drugs for the treatment of T2DM and hyperuricemia respectively and they are likely to be intaken concomitantly in the clinic. CYP2C9 is known to a predominant enzyme in the metabolism of both GLM and BNR. Typically, co-administration multi-drug leaded to variations of drug concentration in plasma through the same metabolic pathway, as it would probably alter the PK parameters of each other, even influencing the efficacy and safety of drugs in clinic. The previous researches of interaction had reported that BNR uninfluenced the pharmacokinetic parameters of allopurinol and oxipurinol in 1982 (Breithaupt *et al.*, 1982), but markedly altered those of allopurinol in 1986 (Colin *et al.*, 1986), such as area under the curve, average plasma concentration, peak level, elimination half-life, mean residential time, renal clearance and fractional excretion. Meanwhile, co-administration of BNR enhanced the anticoagulant action of warfarin, but the pharmacokinetic parameters of this study were unconfirmed further (Shimodaira *et al.*, 1996). In the present study, we focused on the interaction of GLM and BNR in healthy male SD rats *in vivo*, whereas the experimental data were unavailable to demonstrate that GLM changed the PK characteristics of BNR conspicuously.

Our research demonstrated that 0.5 and 1.0mg/kg GLM induced a statistically significant alteration of the PK parameter of BNR: only the $t_{1/2z}$ was notably shortened with being reduced by half and three quarters compared with the control group, respectively. Indeed, the reduction in the $t_{1/2z}$ of BNR indicated a partial influence of two different doses GLM on the bioavailability of BNR, simultaneously reflecting that both 0.5 and 1.0mg/kg GLM accelerated the elimination of BNR *in vivo*, the higher dose of GLM, the faster elimination of BNR. Noteworthily, these findings were in contrast to the theoretical speculation, which presumed that GLM may tend to decrease the elimination of BNR due to the occupancy of the same metabolic CYP2C9 in principle.

Underlying mechanism of drug-drug interaction between GLM and BNR was not fully comprehended. Nevertheless, we could conclude the possible mechanism of this research that the influence of BNR on GLM exposure. First, considering GLM showed a relatively slight affection of drug-drug interaction with BNR was partly explained by CYP2C9 gene of the two drugs being highly polymorphic and its genetic polymorphisms. These two drugs were both substrates of CYP2C9, which had three main allelic isoforms including CYP2C9*1, *2 and *3, remarkably influencing their metabolism and efficacy in clinic (He *et al.*, 2017; Yang *et al.*, 2018). It was demonstrated that CYP2C9*1 crucially acted in the metabolism of BNR, with minor contributions to CYP2C9*2 and CYP2C9*3, yet CYP2C9*2 and CYP2C9*3 displayed higher metabolic activity towards GLM than CYP2C9*1 (Yang *et al.*, 2018). Second, GLM and BNR showed different levels with drug-drug protein binding which is an important factor in drug-drug interaction. GLM has a high affinity for plasma protein, with less than 1% free-drug in plasma (Langtry *et al.*, 1998). The combination of drugs reduced the disruption of BNR in the tissues and finally accelerated its metabolism in plasma, which explained our results further. Finally, the inter-individual differences were wide in the elimination of BNR (Walter-Sack *et al.*, 1988; Walter-Sack *et al.*, 1990). Low- and high-dose effects of GLM intake thus partially altered the pharmacokinetic parameters of BNR in male SD rats.

CONCLUSION

From the results, co-administration of GLM significantly affected the sole pharmacokinetic parameter ($t_{1/2z}$) of BNR due to its different CYP2C9 allelic isoforms and binding affinity of protein. The combination of GLM would accelerate metabolism of BNR and reduce the time to effective therapy. In the absence of any pharmacokinetic interaction between GLM and BNR, we believed that dose adjustment of the two drugs due to their pharmacokinetic interaction was necessary. Despite the study was limited by the relatively small number of rats researched, further studies are needed to confirm the mechanism of drug-drug interaction between GLM and BNR.

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