FULL PAPER

Pharmacology

Borneol influences the pharmacokinetics of florfenicol through regulation of cytochrome P450 1A2 (CYP1A2), CYP2C11, CYP3A1, and multidrug resistance 1 (MDR1) mRNA expression levels in rats

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ABSTRACT. Borneol is a traditional Chinese medicine. In Chinese veterinary clinics, borneol and its related compounds are often used in combination with florfenicol to treat respiratory infections. This study investigated whether the pharmacokinetics of florfenicol in rats was affected by its concomitant use with borneol. Sprague-Dawley rats were intragastrically administered borneol (50 mg/kg body weight (BW)) or 0.5% carboxymethyl-cellulose sodium for 7 consecutive days, and then intragastrically administered florfenicol (25 mg/kg BW) on the eighth day. Pharmacokinetic studies showed that borneol significantly decreased the area under the concentration-time curve from zero to infinity ($AUC_{(0-t)}$), time to reach peak concentration (T_{max}), and the peak concentration (C_{max}) values of florfenicol, whereas the values of mean residence time from zero to infinity ($MRT_{(0-t)}$), elimination half-life ($t_{1/2z}$), apparent volume of distribution fraction of the dose absorbed (Vz), and plasma clearance fraction of the dose absorbed (CLz) were increased significantly. Furthermore, the mRNA expression levels of multidrug resistance 1 (MDR1) and cytochrome P450 3A1 (CYP3A1) in the jejunum and of CYP1A2 and CYP2C11 in the liver were significantly upregulated by borneol. In conclusion, borneol decreased absorption, increased clearance, improved distribution, and increased the mean residence time of florfenicol in rats, possibly through regulating the mRNA expression levels of drug-metabolizing enzymes and efflux transporters.

KEY WORDS: drug-metabolizing enzymes, traditional Chinese medicine, veterinary medicine

Borneol ($C_{10}H_{18}O$), a traditional Chinese medicine, is widely used and has a variety of pharmaceutical effects, including hypoglycemia enhancement, antiviral, antibacterial, anti-tumor, neuroprotective, and anti-angiogenic effects. Previous studies have shown that borneol could enhance the absorption of co-administered drugs in the nasal cavity and gastrointestinal tract, and promote drug distribution to the brain [3, 7, 10, 16, 21, 37]. However, owing to their various physical and chemical properties, the dose of the co-administered drugs, and other factors, the interactions that occur between borneol and co-administered drugs are not always predictable.

Florfenicol is a synthetic broad-spectrum antibiotic with activities similar to those of chloramphenicol and is widely used to control bacterial infections in veterinary practice [26, 29, 31]. Florfenicol has less toxicity and better antibacterial activity than chloramphenicol or thiamphenicol [4, 11, 24]. The pharmacokinetic properties of florfenicol have been documented in many animal species [1, 2, 9, 22, 28, 30], and several studies have reported on the possible metabolic pathways and mechanisms of florfenicol *in vivo*. Liu *et al.* [18] reported that P-gp and/or cytochrome P450 3A (CYP3A) are likely involved in the distribution of florfenicol in rabbits. Wang *et al.* [32] suggested that CYP3A plays a key role in the pharmacokinetics of florfenicol in chickens. In Chinese veterinary clinics, florfenicol is often used in combination with traditional Chinese medicine preparations. In our previous study, we found that anemoside B4, the major effective saponin in *Pulsatillae radix*, could decrease the plasma concentration of florfenicol [14]. In addition, we also found that baicalin could affect the pharmacokinetics of florfenicol in rats and increase the

plasma concentration and residence time of florfenicol [15].

In Chinese veterinary clinics, borneol is often used to treat sore throat and is combined with florfenicol to treat respiratory infections in livestock and poultry. However, the potential for drug-drug interaction between borneol and florfenicol remains unknown. Therefore, to investigate whether a drug-drug interaction occurs between borneol and florfenicol, we assessed the effects of borneol on the pharmacokinetics of florfenicol in rats. The *in vivo* pharmacokinetic properties of florfenicol in rats with or without borneol pretreatment were determined using ultra-high-performance liquid chromatography (UHPLC). In addition, the effects of borneol on CYP1A2, CYP2C11, and CYP3A1 mRNA expression in the rat liver, as well as that of CYP3A1 and multidrug resistance 1 (MDR1) in the rat jejunum were analyzed using real-time PCR. Our results can be useful to predict the clinical effects of borneol-florfenicol interactions.

MATERIALS AND METHODS

Chemicals and reagents

Synthetic borneol (96% (+)-borneol) was purchased from Guangzhou Huangpu Chemical Industrial Group Co., Ltd. (Guangzhou, PR China). Florfenicol was supplied by Sichuan Dingjian Animal Pharmaceutical Co., Ltd. (Chengdu, PR China). Synthetic borneol and florfenicol were each suspended in 0.5% carboxymethyl-cellulose sodium (CMC-Na) solution (Chengdu Chron Chemicals Co., Ltd., Chengdu, PR China). Florfenicol and chloramphenicol (internal standard) analytical standards were obtained from the China Institute of Veterinary Drug Control (Beijing, PR China). Acetonitrile and methanol ethyl acetate were HPLC-grade (Merck Chemicals Co., Ltd., Darmstadt, Germany). All other chemicals were of analytical grade or better.

Animals

Male Sprague-Dawley rats (220 ± 20 g), license number SCXK2015-030, were obtained from Chengdu Dashuo Experimental Animal Co., Ltd. (Chengdu, PR China). The rats were housed at the Laboratory Animal Research Center of Sichuan Animal Science Academy in house cages under standard laboratory conditions (22 ± 2°C and a natural light-dark cycle). The rats were fed a regular rodent diet and allowed free access to water during a 1-week acclimatization period prior to being used for experiments. All experimental procedures and protocols in this study were reviewed and approved by the Animal Ethics Committee of Sichuan Animal Science Academy, and all procedures were performed in accordance with principles outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals [23].

UHPLC for detection of florfenicol in plasma

UHPLC analyses were performed using an UltiMate 3000 HPLC (Thermo Fisher Scientific Inc., Chelmsford, MA, USA) as previously described [13]. A Diamonsil C18 column (4.6 mm × 250 mm, 5 μm; Thermo Fisher Scientific Inc.) was used to simultaneously detect florfenicol and chloramphenicol at a constant temperature of 40°C. The mobile phase consisted of acetonitrile and water (27:73, v:v) at a flow rate of 1.0 ml/min, and the injection volume was 20 μl. The detection wavelength was set at 223 nm, and the overall run time of the analysis was 16 min.

Method validation studies were performed for the following variables: limit of detection (LOD), limit of quantification (LOQ), precision, extraction recovery, and correlation coefficients of the calibration curves.

The LOD and LOQ were detected based on signal-to-noise ratios of 3 and 10, respectively. Precision was estimated by the intra-day and inter-day precision obtained on 3 days when using 3 standard levels of each analyte (0.1, 2.5, and 20 μg/ml). Extraction recovery was expressed as the ratio of the mean area of florfenicol in plasma samples to that of the analytes in neat standard samples at equivalent concentrations. The standard curve for florfenicol was derived from the ratios of the peak-areas of florfenicol and the internal standard chloramphenicol (S), and plotting these against the corresponding concentrations of florfenicol in blank plasma (C). Standard samples of florfenicol were prepared at concentrations of 50, 20, 10, 5.0, 2.5, 0.5, 0.1, and 0.05 μg/ml, with parallel processing of five samples each.

The LOQ and LOD of florfenicol were validated at 0.06 and 0.02 μg/ml, respectively. The variations in intra-day and inter-day assay precision determined at three standard levels were less than 6.2%. The extraction recoveries at three concentrations of florfenicol all exceeded 82.0%. The correlation coefficient (R^2) for the calibration curve was 0.9992 (Fig. 1).

Effect of borneol on the pharmacokinetics of florfenicol in rats

Study design, formulation, and dosing regimen: A total of 12 rats were randomly assigned to two separate groups (six rats per group): a control group that was administered 0.5% CMC-Na and a borneol treatment group that received synthetic borneol (50 mg/kg body weight (BW)). The borneol suspension was intragastrically administered during the morning on 7 consecutive days, and the same volume of 0.5% CMC-Na was orally administrated by tube gavages to rats in the control group. During the entire trial period, there were no significant differences in food intake, growth, or health status between rats in the borneol and control groups.

Pharmacokinetic study

On the eighth day, after fasting for 12 hr, a suspension containing florfenicol (25 mg/kg BW) [15] was intragastrically administered to all rats in both groups. Blood samples (200 μl) from each rat were collected via the oculi chorioideae vein at 0.083, 0.25, 0.50, 0.75, 1, 2, 4, 6, 8, 10, 12, and 24 hr after administration of florfenicol. Plasma samples were obtained by centrifugation at 4,000 rpm for 5 min and then stored at −80°C until UHPLC analysis.

Sample preparation

Plasma samples were prepared as previously described [15]. Next, a 100 µl aliquot of thawed plasma in a 2 ml centrifuge tube was spiked with 5 µg of chloramphenicol (internal standard) in 10 µl of methanol and then added to 400 µl of ethyl acetate. The tube was vortex mixed for 2 min, and the sample was centrifuged at 4,000 rpm for 10 min at 25°C. The supernatant was transferred to a new tube, and the subnatant was re-extracted with 800 µl of ethyl acetate solution to collect a second extract. The pooled supernatant was evaporated to dryness under a flow of nitrogen at 40°C; after which, the residue was dissolved in 100 µl of mobile phase and centrifuged at 12,000 rpm for 10 min at 4°C. Finally, 20 µl of supernatant was injected into the UHPLC system for analysis.

Effect of borneol on the expression of mRNA for drug-metabolizing enzymes/efflux transporters

Drug administration and sample collection: Another 12 rats were randomly assigned to two separate groups (six rats per group). The study design, formulations used, and dosing regimen were the same as those described above (Effect of borneol on the pharmacokinetics of florfenicol in rats). On the eighth day, after being fasted for 12 hr, rats were euthanized with ether. Samples of the liver and jejunum tissue were removed quickly, perfused with ice-cold saline to remove blood residue, blotted dry, and stored at −80°C.

Total RNA isolation and synthesis of cDNA: The total RNA was extracted from each sample using the TRIzol reagent (Invitrogen Corp., Carlsbad, CA, USA) according to the manufacturer's protocol. The concentration, purity, and integrity of the total RNA samples were measured as previously reported [13]. Single-stranded cDNA was synthesized from 5 µl of total RNA using RevertAid Premium Reverse Transcriptase (Thermo Fisher Scientifc Inc.) and a C100 PCR instrument (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The products were stored at −80°C until analysis.

Real-time RT-PCR analysis: Real-time RT-PCR was performed using an ABI StepOne RT-PCR instrument (Applied Biosystems, Foster City, CA, USA) and a 20 µl reaction mixture that contained 10 µl of High Rox Sybr Green qPCR Master Mix (Sangon Biotech Co., Ltd., Shanghai, PR China), 2 µl of cDNA, 0.4 µl of each oligonucleotide primer (10 µM), and 7.2 µl of diethyl pyrocarbonate-treated autoclaved distilled water. The PCR protocol consisted of initial denaturation at 95°C for 3 min, followed by 40 cycles of denaturation at 95°C for 7 sec, annealing at 55°C for 10 sec, extension at 72°C for 15 sec, and a final extension at 72°C for 5 min. Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) served as a house-keeping gene. The data were analyzed using the $2^{-(\Delta\Delta Ct)}$ method [19], and results are expressed as the fold-change in gene expression relative to that of the control. The sequences of the forward and reverse primers are listed in Table 1.

Statistical analysis

Data Analysis System software (Version 3.0, Chinese Pharmacological Society, Beijing, PR China) was used to calculate values for the pharmacokinetic parameters of florfenicol using a noncompartmental method. The area under the concentration–time curve (AUC) was calculated using the trapezoidal rule method. The area under the first moment curve (AUMC) was defined as the area under the product of the time and drug concentration–time curve and was also calculated using the trapezoidal rule method. Mean residence time (MRT) was calculated using the equation MRT=AUMC/AUC. The elimination rate constant (λz) was estimated by linear regression analysis of the terminal data points, and the elimination half-life ($t_{1/2z}$) was calculated using the equation $t_{1/2z}=0.693/\lambda z$. The peak plasma concentration (C_{max}) and peak plasma time (T_{max}) were obtained directly. Total body clearance (CLz) was calculated as CLz=Dose/AUC. The apparent steady-state volume of distribution (Vz) was calculated as Vz=CLz/Zeta.

All data are presented as mean ± standard deviation. Significant differences between the groups were evaluated using one-way ANOVA performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). For all analyses, a *P*-value <0.05 was considered to be significant.
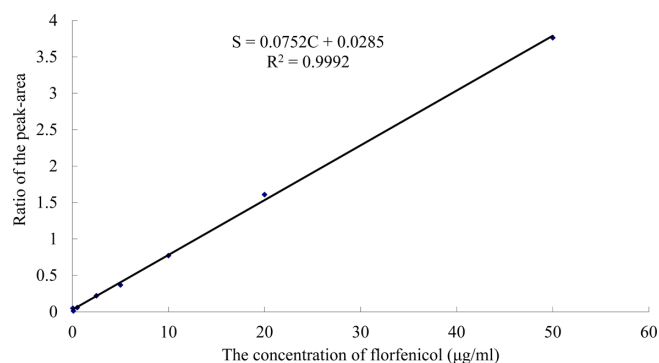

Fig. 1. Standard curve for plasma florfenicol concentrations. S: ratios of the peak-areas of florfenicol and the internal standard (chloramphenicol); C: corresponding concentration of florfenicol in blank plasma.

Table 1. Sequences of the forward and reverse primers used for RT-PCR

Enzymes	Forward	Reverse
CYP1A2	5′-GAATGTCACCT CAGGGAATGC-3′	5′-GACCGCCATTG TCTTTGTAGTT-3′
CYP2C11	5′-GAGGACCATTG AGGACCGTATT-3′	5′-GGAGCACAGC CCAGGATAAA-3′
CYP3A1	5′-TTCCATCTTAT GCTCTTCACCG-3′	5′-ACCTCATGCCA ATGCAGTTC-3′
MDR1	5′-TCCTATGCTGC TTGTTTCCG-3′	5′-AGACTTTGGCC TTCGCGTA-3′
GAPDH	5′-CAAGTTCAACG GCACAGTCAA-3′	5′-CGCCAGTAGAC TCCACGACA-3′

CYP, cytochrome P450; MDR, multi drug resistance; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase.

RESULTS

Effect of borneol on the pharmacokinetics of florfenicol

The plasma concentrations of florfenicol in rats at each time point are listed in Table 2. After intragastric administration of borneol for 7 consecutive days, the plasma concentrations of florfenicol at time points ranging from 0.083 hr to 8 hr were lower than the corresponding concentrations in the control group, with significant decreases being detected at 0.50, 0.75, 1, 2, and 4 hr. In contrast, the plasma concentrations of florfenicol at 10, 12, and 24 hr in the borneol-treated group were higher than the corresponding concentrations in the control group, with significant increases being detected at 12 and 24 hr.

The effects of borneol on the pharmacokinetics of florfenicol in rats are presented in Table 3 and Fig. 2. After intragastric administration of borneol for 7 consecutive days, the values for $AUC_{(0-t)}$, T_{max}, and C_{max} were significantly decreased by 30.39%, 44.67%, and 52.90%, respectively, when compared with the corresponding values in the control group, whereas the values for $MRT_{(0-t)}$, $t_{1/2z}$, Vz, and CLz in the borneol-treated group were significantly increased by 68.38%, 161.88%, 275%, and 44.83%, respectively, when compared with their corresponding values in the control group.

Effect of borneol on mRNA expression for drug-metabolizing enzymes/efflux transporters

The effects of borneol on the levels of CYP1A2, CYP2C11, and CYP3A1 mRNA expression in the liver are shown in Fig. 3A.

Table 2. Plasma concentrations of florfenicol in rats at each time point after intragastric administration of florfenicol (25 mg/kg body weight (BW)) with or without synthetic borneol (50 mg/kg BW for 7 consecutive days) pretreatment (n=6, mean value ± standard deviation)

Time/hr	Plasma concentrations of florfenicol (µg/ml)	
	Control group	Borneol group
0.083	2.19 ± 1.12	1.69 ± 0.93
0.25	4.37 ± 0.37	4.13 ± 1.92
0.50	12.27 ± 4.69	7.60 ± 1.67 [a]
0.75	13.69 ± 2.65	9.45 ± 1.92 [a]
1.00	18.79 ± 7.10	9.52 ± 1.28 [a]
2.00	18.30 ± 2.86	8.05 ± 1.58 [a]
4.00	8.89 ± 0.89	5.28 ± 1.67 [a]
6.00	5.04 ± 1.23	3.45 ± 1.08
8.00	2.28 ± 0.45	1.99 ± 0.50
10.00	0.93 ± 0.11	1.15 ± 0.18
12.00	0.40 ± 0.10	0.89 ± 0.12 [a]
24.00	0.42 ± 0.09	1.13 ± 0.19 [a]

a) Significantly different from the control group, $P<0.05$.

Table 3. Pharmacokinetic characteristics of florfenicol in the plasma of rats after intragastric administration of florfenicol (25 mg/kg BW) with or without borneol (50 mg/kg BW for 7 consecutive days) pretreatment (n=6, mean value ± standard deviation)

Characteristic	Control Group	Borneol Group
$AUC_{(0-t)}$ (mg/l*hr)	86.32 ± 6.86	60.09 ± 9.49 [a]
$MRT_{(0-t)}$ (hr)	4.08 ± 0.16	6.87 ± 0.59 [a]
$t_{1/2z}$ (hr)	1.60 ± 0.18	4.19 ± 1.96 [a]
T_{max} (hr)	1.50 ± 0.58	0.83 ± 0.20 [a]
Vz (l/kg)	0.68 ± 0.12	2.55 ± 1.29 [a]
CLz (l/hr/kg)	0.29 ± 0.02	0.42 ± 0.07 [a]
C_{max} (mg/l)	21.57 ± 3.81	10.16 ± 1.54 [a]

a) Significantly different from the control group, $P<0.05$. $AUC_{(0-t)}$, area under the concentration-time curve from zero to infinity; $MRT_{(0-t)}$, mean residence time from zero to infinity; $t_{1/2z}$, elimination half-life; T_{max}, time to reach peak concentration; Vz, apparent volume of distribution fraction of the dose absorbed; CLz, plasma clearance fraction of the dose absorbed; C_{max}, peak concentration.
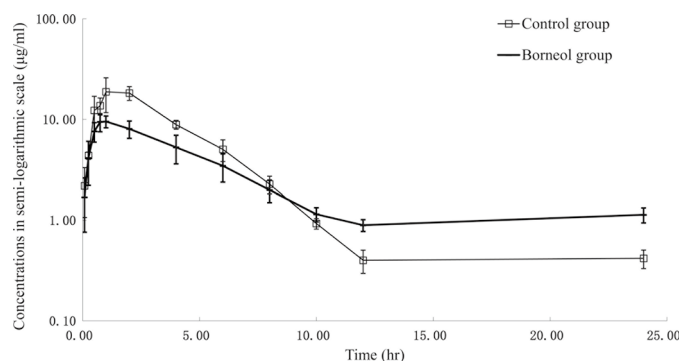

Fig. 2. Semi-logarithmic plots of mean plasma concentration–time profiles of florfenicol in rats after intragastric administration of florfenicol (25 mg/kg body weight (BW)) with or without borneol (50 mg/kg BW for 7 consecutive days) pretreatment. Each symbol with a bar represents the mean value ± standard deviation of six rats.
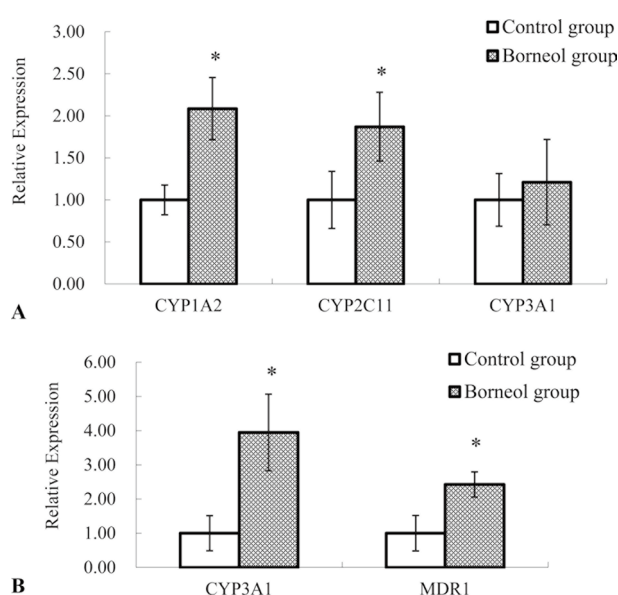

Fig. 3. Effect of borneol administration (50 mg/kg BW for 7 consecutive days) on cytochrome P450 1A2 (CYP1A2), CYP2C11, and CYP3A1 mRNA expression in the liver (A), and CYP3A1 and multi drug resistance (MDR) 1 mRNA expression in the jejunum (B) (n=6). *Significantly different from the control group, $P<0.05$.

After intragastric administration of borneol for 7 consecutive days, the levels of CYP1A2 and CYP2C11 mRNA expression in the borneol-treated group were significantly increased by 2.09-fold and 1.87-fold, respectively, when compared with their levels in the control group. However, the levels of CYP3A1 mRNA expression in the borneol-treated group were not significantly different from those in the control group.

The effects of borneol on the levels of CYP3A1 and MDR1 mRNA expression in the jejunum are presented in Fig. 3B. After intragastric administration of borneol for 7 consecutive days, the levels of CYP3A and MDR1 mRNA expression in the jejunum were significantly increased by 3.95-fold and 2.43-fold, respectively, relative to their levels in the control group.

DISCUSSION

In the present study, rats pre-treated with borneol had lower plasma concentrations of florfenicol at all time points during the absorption phase than rats that were not pre-treated with borneol. These differences reflected the decreased rate of florfenicol absorption in the intestine. In addition, considering the significant decreases in the C_{max} and $AUC_{(0-t)}$ values of florfenicol, these differences also reflected the significant decrease in florfenicol absorption among rats in the borneol-treated group. These results are similar to those reported by Zou et al. [38]; however, the co-administered drugs used in that study were different. P-gp, an important transport protein, is the product of the multiple drug resistance (MDR) gene 1 [30] and is expressed in the intestine along with CYP3A to form a transport barrier to drug absorption [20, 25]. In our study, the levels of jejunal MDR1 and CYP3A1 mRNA expression in the borneol-treated rats were significantly increased, which may have induced the activities of P-gp and CYP3A1, leading to increased metabolism and an efflux of florfenicol into the intestinal cavity. Thus, the absorption of florfenicol was decreased. This speculation is consistent with the altered pharmacokinetics of florfenicol that we observed.

Although several studies have examined the effect of borneol on drug-metabolizing enzymes/efflux transporters or the absorption of co-administered drugs, the results of those studies are not consistent with each other. He et al. [10] suggested that borneol inhibits the P-gp-mediated efflux system, and thereby improves the intestinal absorption of drugs. Wang et al. [33] reported that borneol increases the absorption rate and apparent permeability coefficient of Rho-123 in the rat jejunum and ileum. Zhao et al. [37] used borneol as both a P-gp inhibitor and absorption enhancer to improve the absorption of olerciamide A in rats. However, Zou et al. [38] reported that the T_{max} and C_{max} of berberine were significantly reduced after co-administration of borneol in rats [38]. Ru et al. [27] reported that borneol could only promote the gastrointestinal absorption of small nanoparticles and had no effect on the absorption of drugs with a particle size greater than 100 nm. Lei et al. [12] suggested that the effects of borneol on CYP3A4 and P-gp are significantly different and may be related to the optical rotation of borneol, as well as the dose of borneol and time of its administration. In the present study, the decreases in florfenicol absorption and absorption rate and increases in jejunal P-gp and CYP3A1 mRNA expression that were detected in borneol-treated rats may have been related to the particle size of florfenicol (>100 nm) used and the dose or time of its administration; however, these possibilities require further investigation.

CYP450 is the most important phase I metabolic enzyme in the liver and is mainly located in the endoplasmic reticulum of hepatocytes. In the present study, rats pre-treated with borneol had increased levels of mRNA expression for three CYP450 subenzymes, and the levels of CYP1A2 and CYP2C11 mRNA were increased significantly. We speculate that these changes in mRNA expression may serve to enhance the activity levels of the corresponding drug-metabolizing enzymes. Although there have been few reports concerning the mechanism by which florfenicol is metabolized in rats, Liu [17] suggested that CYP1A plays a major role in the metabolism of florfenicol in rats. In our study, the levels of CYP1A2 expression in borneol-treated rats were significantly increased, which may have increased the phase I metabolism rate of florfenicol. These increases may have also been the main factor contributing to the decreased clearance rate of florfenicol in those rats (the CLz values of florfenicol in borneol-treated rats were significantly increased when compared with those in control rats). In addition, Chen et al. [5, 6] reported that the oral administration of borneol to rats for 7 consecutive days significantly increased CYP2B/D mRNA expression, protein expression, and hepatic CYP2B/D activity, thereby increasing the clearance rate and decreasing the AUC of co-administered synthetic drugs. These findings were consistent with the results of our study, and further showed that borneol could induce the expression or activity of CYP2 enzymes in the liver. However, the activities of rat CYP450 enzymes were not measured in our current study, which makes it impossible to fully support the above inference. Therefore, the validity of this inference requires further investigation.

We found that the values for Vz in the borneol-pretreatment group were significantly higher than those in the control group (the mean Vz value in the borneol-treated group was increased by 275%), indicating that the tissue distribution of florfenicol was significantly increased after pretreatment with borneol. We speculate that the increase in the tissue distribution of florfenicol may be the major reason for the higher plasma concentrations of florfenicol detected at 12 hr and 24 hr in the borneol-treated group and may also have caused the significant increases in the $MRT_{(0-t)}$ and $t_{1/2z}$ values of florfenicol that group. Numerous studies have reported that borneol can enhance the distribution of co-administered synthetic drugs into tissues, such as the kidney and brain [3, 8, 34–36]. Our findings are similar to those reported in these previous studies. Based on the results of this study, we will continue to examine the effects of borneol on the tissue distribution of florfenicol in vivo.

In this study, the $AUC_{(0-t)}$ values of florfenicol in the borneol-pretreatment group were significantly decreased when compared to the corresponding values in the control group. This observation suggests that borneol administration reduces the prophylactic or therapeutic effectiveness of florfenicol. In addition, this study also indicated that borneol could significantly induce MDR1 and CYP3A1 mRNA expression in the jejunum, as well as CYP1A2 and CYP2C11 mRNA expression in the liver. These findings emphasize the need for caution when co-administering a traditional Chinese medicine containing borneol in conjunction with chemical drugs that are metabolized by the above-mentioned drug-metabolizing enzymes and/or efflux transporters.

In conclusion, this study evaluated the effects of borneol on the pharmacokinetics of the antibiotic florfenicol, and examined the effects of borneol on CYP1A2, CYP2C11, CYP3A1, and MDR1 mRNA expression in rats. We found that borneol affected the pharmacokinetics of florfenicol, decreased absorption, increased clearance, improved distribution, and increased the mean residence time of florfenicol, probably by significantly increasing MDR1 and CYP3A1 mRNA expression in the jejunum and significantly increasing CYP1A2 and CYP2C11mRNA expression in the liver. The results of these experiments in rats should prompt additional studies on the effects of borneol when used in conjunction with various pharmaceutical agents in veterinary medicine.

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