Population Pharmacokinetics Study of Nemonoxacin Among Chinese Patients With Moderate Hepatic Impairment

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ABSTRACT

Purpose: Nemonoxacin is a novel C-8-methoxy nonfluorinated quinolone that has been approved for the treatment of community-acquired pneumonia (CAP) in adults. The goals of this study were to evaluate the pharmacokinetic (PK) and population PK parameters of nemonoxacin and to provide the appropriate dose adjustment recommendations for patients with hepatic impairment.

Methods: An open-label, single-dose, parallel group (moderate hepatic impairment group and healthy control group) PK study of nemonoxacin was conducted. Liquid chromatography–tandem mass spectrometry (LC-MS/MS) was performed to detect the unchanged nemonoxacin concentration in blood and urine samples. The nonlinear mixed effects modeling tool NONMEN (version 7.3) was used to conduct the population PK analysis. The paired-t test was conducted to compare the PK parameters of the hepatic impairment group and the healthy control group by SPSS (Version 17.0).

Findings: Ten subjects for each group were enrolled into the PK study. The PK parameters as well as the plasma concentration-time and logarithmic concentration-time profiles after taking a 500-mg single dose of nemonoxacin showed few differences between the two groups ($P > 0.05$). The mean areas under the plasma concentration vs. time curve from 0 to 72 h (AUC0-72 h) of the moderate hepatic impairment group and the healthy control group in the nemonoxacin PK study were 58.50 (17.30) mg·h/mL and 49.74 (10.16) mg·h/mL, respectively, giving a mean (SD) AUC0-72 h ratio of 1.15 (0.42) with a 90% CI of 0.91–1.39. A 3- compartment model was considered to be the best model for the data, especially in fitting the plasma point at low drug concentrations. Covariate analysis indicated that weight affected CL/F, V1/F, and V3/F and that eGFR only affected CL/F in the power function model, while gender affected V3/F in the linear model by forward selection and backward deletion.

Implications: The population PK parameters of nemonoxacin were evaluated in patients with hepatic impairment. The hepatic function did not have a significant impact on the PK parameters of nemonxacin, but renal function was a meaningful covariate that is consistent with its PK characteristics. In this study, nemonoxacin was well tolerated in the patients with moderate hepatic impairment as well as in the healthy subjects. Based on these data, it is not necessary to consider dose adjustment of nemonoxacin in patients with mild or moderate hepatic impairment. ClinicalTrials.gov identifier: NCT02604498. (*Clin Ther*. 2019;41:505–517)

Keywords: hepatic impairment, nemonoxacin, pharmacokinetics, population pharmacokinetics, dose adjustment.

INTRODUCTION

Nemonoxacin is a novel C-8-methoxy nonfluorinated quinolone antibiotic that has recently undergone

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clinical trials. It harbors the same mode of action as its structural analogues levofloxacin and moxifloxacin by targeting topoisomerase II and IV to inhibit DNA replication and cell division of bacteria.[1] Compared with its fluorinated analogues levofloxacin and moxifloxacin, nemonoxacin displays more potent and broad-spectrum activities against both gram-positive and gram-negative bacteria and has a reduced incidence of toxic side effects due to the absence of the fluoride residue. Moreover, nemonoxacin exhibits potent activities against various drug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, ciprofloxacin-resistant MRSA, and levofloxacin-resistant *S. pneumoniae*.[2,3] In clinical trials, it has been shown that 750 or 500 mg of nemonoxacin taken once daily is an effective and safe therapeutic dose to replace levofloxacin for the treatment of community-acquired pneumonia (CAP).[4,5] Nemonoxacin has been approved by the US Food and Drug Administration as a qualified infectious disease product for CAP as well as acute bacterial skin and skin-structure infections. In October 2016, the China Food and Drug Administration approved nemonoxacin malate capsules as a clinical drug for the treatment of CAP in adults.

Previously, nemonoxacin was shown to have a well-tolerated profile in a pharmacokinetics (PK) study of healthy Chinese subjects. The PK profile supported the therapeutic plan of a continuous once-daily dose of 500 mg of nemonoxacin for treating Chinese patients with CAP who had normal hepatic and renal function.[6] Phase I to Phase IV clinical trials indicated that nemonoxacin malate was rapidly absorbed into the human body, with a high bioavailability (100%) and a linear association between the PK profile and an intake dose of 250−750 mg; in addition, there was no evidence of drug accumulation. The absorption degree of nemonoxacin was affected by fasting and fed conditions. In the fed state, both the C_{max} and AUC_{0-24h} of nemonoxacin decreased, and the T_{max} increased twofold from 1.31 to 3.07 h. Nemonoxacin is widely distributed throughout the whole body, and ~16% of it binds to human plasma proteins.[6−8] No or few metabolites (<5% in rat hepatocytes) of nemonoxacin were found in previous *in vitro* metabolism studies.[9] The elimination $t_{1/2}$ of nemonoxacin is 10−12 h, and it is excreted primarily by the renal metabolic pathway. Furthermore, the amount of unchanged nemonoxacin, which was tested by a urinary recovery assay in Chinese volunteers, was found to be retained at ~60%−70% of the whole intake dose over 72 h.[6]

In China, liver diseases affect ~300 million people.[10] Hepatic impairment in China is mainly caused by hepatitis virus−induced cirrhosis,[11] as shown by the finding that hepatitis B and C infections exhibit a positive correlation between the trend of incidence and the ages of patients.[12] We therefore conducted the present study, an open-label, single-dose, parallel-group (moderate hepatic impairment group and healthy control group) PK analysis of nemonoxacin among patients with moderate hepatic impairment.

SUBJECTS AND METHODS

This study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki as well as the Good Clinical Practice guidelines. It was approved by the Independent Ethics Committee of Huashan Hospital, Fudan University, on October 26, 2015 (no. 2015-247). This study was a single-center trial.

Study Subjects

The moderately impaired hepatic function of the patients enrolled in this study was usually induced by cirrhosis that was caused by various types of pathogenesis, including viral hepatitis, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, and other factors. According to the Child-Pugh classification, moderate hepatic impairment was determined to be level B hepatic dysfunction. The key inclusion criteria of the hepatic impairment group included the following: male or female subjects, aged 18−70 years, a body mass index (BMI) of 17−30 kg/m^2, an estimated glomerular filtration rate (eGFR) > 50 mL/min/1.73 m^2 (calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation), and a healthy body state, which was determined by medical history and physical examination (including vital signs, laboratory testing, B ultrasonography, and chest radiograph).[13] The key exclusion criteria included the following situations of the diseased subjects: having acute disease or chronic disease that may affect the PK profile of the drug *in vivo* except for hepatic function impairment; having a history of clinically significant cardiovascular, neurologic, psychiatric,

gastrointestinal, pulmonary, renal, or endocrine disease within 1 year of the PK study; having acute or subacute hepatic function failure; having a total bilirubin content >3 × the upper limit of the normal level (ULN) without cholestasis, alkaline phosphatase levels >2 × ULN, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >5 × ULN; an international normalized ratio ≥1.5 or prothrombin time activity ≤40%; use of another investigational or clinically used drug that can damage hepatic function within 3 months before dosing; having clinically significant abnormal 12-lead ECG results, including atrioventricular block, torsades de pointes ventricular tachycardia, and other types of ventricular tachycardia, ventricular fibrillation, ventricular flutter, T-wave change with clinical significance, or any abnormal results that affect QTc during the PK screening.

The healthy control subjects were chosen to be included in this study if their sex, age (±5 years), and BMI (±15%) matched those of the patients with hepatic impairment. The key exclusion criteria for the healthy control subjects were as follows: a history of acute or chronic disease, including chronic liver, renal, cardiovascular, neurologic, psychiatric, gastrointestinal, pulmonary, urinary, or endocrine disease; the use of drugs that may affect the function of liver metabolism enzymes within 30 days before dosing or taking medications of the investigational drug PK study that may affect the PK profile during the experimental procedure; the use of antibiotics, glucocorticoids, or immunosuppressive agents that may damage organs within 14 days before dosing; clinically significant abnormal 12-lead ECG results, including atrioventricular block, torsades de pointes ventricular tachycardia, and other types of ventricular tachycardia, ventricular fibrillation, ventricular flutter, T-wave change with clinical significance, or QTc >450 ms; and an abnormal laboratory test result with clinical significance as assessed by an investigator during the screening procedure.

The subjects from both groups agreed to remain in the ward for 24 h before dosing and promised not to consume coffee, tea, chocolate, alcohol, grapefruit juice, orange juice, or other food or drinks containing caffeine or xanthine. In addition, enrolled subjects signed an informed consent form of their own accord.

Study Design

An open-label, single-dose, parallel-group PK study for nemonoxacin was conducted in Huashan Hospital, Fudan University. Nemonoxacin malate capsule (manufactured by Zhejiang Medicine Co, Ltd, Zhejiang, China) was orally administered at a single dose of 500 mg. A screening visit for all subjects occurred within 14 days before nemonoxacin administration. The subjects entered the trial center 1 day before nemonoxacin administration and remained until 72 h after taking the drug. Blood samples were collected at the following time points: 1 h~0 h predose, and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, and 72 h after dosing. Meanwhile, urine samples were collected at the following time points: 12 h~0 h predose and 4, 8, 12, 24, 48, and 72 h after dosing.

Safety Assessment

The tolerability and safety of nemonoxacin were evaluated by checking the prevalence and severity of adverse events (AEs) during the PK study via vital signs, laboratory testing (hematology, clinical chemistry, and urinalysis), physical examination, and 12-lead ECG. A final safety follow-up visit was conducted at 72 h after the administration of nemonoxacin. An additional safety follow-up visit after the final one was performed if necessary.

Analytical Method

LC-MS/MS was conducted to detect the unchanged nemonoxacin concentration in both the blood and urine samples. The lower detection limit of quantitation was 0.005 μg/mL. The blood and urine samples were stored at −40 °C and −80 °C before analysis, respectively.[14]

Statistical Analysis

Phoenix WinNonlin version 6.3 (Certara, Princeton, New Jersey) was used to analyze the PK profile of nemonoxacin by noncompartmental analysis (NCA). The following PK parameters for detecting unchanged nemonoxacin were determined: C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, the mean residence time, total clearance of the drug from plasma (CL/F), apparent volume of distribution (V/F), cumulative amount of unchanged drug excreted into the urine (Ae_{0-24h} and Ae_{0-72h}), and renal clearance of the drug from plasma. The mean

and SD were used to describe the demographic characteristics of the 2 groups and the PK parameters in this study. The associated 90% CIs were determined for each study group. The AUC ratios and their associated 90% CIs were within the range of 0.8−1.25, representing no clinically meaningful change for nemonoxacin plasma exposure, according to previous PK studies and the guidance of PK in patients with impaired hepatic function.[15] The paired *t* test was conducted to compare the PK parameters of the hepatic impairment group and the healthy control group by using SPSS version 17.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

Population PK Model Building

PK analysis was conducted by using the nonlinear mixed effects modeling software NONMEM version 7.3 (ICON Development Solutions, San Antonio, Texas). The model was based on the first-order conditional estimation method with η-ε interaction. Model selection was based on the results of the likelihood ratio tests, residual analysis, and parameter rationalities. The parameter rationalities were estimated based on the residual standard error (RSE) of the parameters in the model. The total RSE of the estimated PK parameters was <40%, and the RSE of key parameters was <30%, which are acceptable values for the final model. Covariate analysis was conducted after the base model selection. Scatter plots of the parameters were estimated from the selected base model and potential covariates, which were plotted to explore the covariate−parameter relationships. The covariates that had a significant impact on the PK parameters ($P < 0.05$) were enrolled into the stepwise method. Potential covariates included the group, oral antiviral agent administered, diuretic agents, symptomatic treatment, sex, weight, BMI, ALT, AST, gamma-glutamyl transferase, ascites, total bilirubin level, prothrombin time, Child-Pugh score, and eGFR. The module of the stepwise covariate model created by Perl-speaks-NONMEM software (version 3.4.2; Uppsala University, Uppsala, Sweden) was then used for covariate screening and identification.[16] Covariate relationships, such as linear function, exponential function, and power function, were assessed for the continuity of covariates, and a stepwise approach was used to evaluate the effects of the covariates. The statistical criteria for a covariate to be incorporated into the model were a decrease >3.84 in the objective function value (OFV) ($P = 0.05$, χ^2 distribution with 1 *df*) of the forward step and an increase <6.63 in the OFV ($P = 0.01$, χ^2 distribution with 1 *df*) of the backward step. A decrease in the OFV >6.63 was considered statistically significant.

The goodness of fit was evaluated by comparing the following graphs both in the base model and in the final model: observed concentrations versus population predictions, observed concentrations versus individual predictions, conditional weighted residuals versus time, and conditional weighted residuals versus population predictions. A bootstrap resampling technique including 1000 samples was used for model validation. A visual predictive check was used to assess the appropriateness of the compartment model graphically because the important ability of the model is to simulate the original data in a similar manner. Compared with the observed data, the concentration profiles were simulated 1000 times to evaluate the predictive performance of the model. The AUC_{0-72h} of individuals and the changes in AUC_{0-72h} based on the Child-Pugh score were simulated by the PK parameters; the intra-individual and interindividual variability findings were obtained based on the final model.

RESULTS

Study Population

Ten subjects for each group were enrolled into the PK study, and they all completed the study. The subjects in the healthy control group matched the 10 subjects in the hepatic impairment group in terms of age, sex, and BMI. The demographic characteristics of the subjects in each group are listed in Table I. The 5 male subjects and 5 female subjects who were enrolled in the hepatic impairment group had liver cirrhosis mostly caused by hepatitis B infection, except for 1 subject who had drug-induced hepatic impairment. The Child-Pugh score was assessed as 7 for eight subjects and as 8 for the other two subjects. All 10 subjects from the hepatic impairment group and 2 subjects from the healthy control group reported taking concomitant medications (Table II).

Table I. Demographic characteristics of the subjects in the moderate hepatic impairment group and in the healthy control group.

Characteristic	Hepatic Impairment Group (n = 10)	Healthy Control Group (n = 10)
Male, no. (%)	5 (50)	5 (50)
Age, mean (SD) [range], y	54.10 (9.31) [38.00–65.00]	54.30 (11.25) [37.00–69.00]
Weight, kg	67.43 (14.28) [49.00–92.00]	63.71 (10.03) [46.00–75.00]
Height, m	1.67 (0.08) [1.58–1.80]	1.63 (0.08) [1.50–1.76]
BMI, kg/m^2	23.92 (3.15) [19.62–28.40]	23.87 (2.51) [18.90–28.20]
Liver function, no. (%)		
Normal	0	10 (100)
Child-Pugh score of 7	8 (80)	0
Child-Pugh score of 8	2 (20)	0
Child-Pugh score of 9	0	0
eGFR, mL/min/1.73 m^2	98.00 (5.73) [88.00–105.00]	101.10 (13.44) [75.00–118.00]
Antiviral agent, no. (%)	8 (80)	0

BMI = body mass index; eGFR = estimated glomerular filtration rate. Values are given as mean (SD) [range], unless otherwise indicated.

Noncompartmental Analysis

The PK parameters (Table III) as well as the plasma concentration–time and logarithmic concentration–time profiles (Figure 1) after taking a 500-mg single dose of nemonoxacin revealed few differences between the 2 groups. The nemonoxacin AUC_{0-72h} values of the moderate hepatic impairment group and the healthy control group were 58.50 (17.30) μg · h/mL and 49.74 (10.16) μg · h/mL, respectively.

The AUC_{0-72h} ratio of the hepatic impairment group to the healthy control group was 1.15 (0.42) (geomean [SD]; range, 0.80–2.42), and the 90% CI was 0.91–1.39 according to NCA.

The mean Ae_{0-24h} ratios (Figure 2) of the moderate hepatic impairment group and the healthy control group were 44.53% (9.87%) and 54.95% (10.53%), respectively. The mean Ae_{0-72h} ratios of the moderate hepatic impairment group and the healthy control group were 53.04% (9.62%) and 63.80% (10.21%) ($P = 0.012$).

Safety

Nemonoxacin was well tolerated in the patients with moderate hepatic impairment as well as in the healthy subjects. No serious AEs were reported in either group (Table IV). All 10 of the AEs reported from 6 subjects with moderate hepatic impairment were related to mild changes in laboratory test results, including a decreased white blood cell count (1 subject), a decreased platelet count (2 subjects), an increased total bilirubin level (2 subjects), an increased ALT level (1 subject), an increased AST level (1 subject), a mild T-wave change (1 subject), and a prolonged QT interval (2 subjects). Five AEs were reported in 3 healthy subjects, including headache (1 subject), ventricular premature beat (1 subject), T-wave changes (2 subjects), and sinus bradycardia (1 subject). All the AEs from those with moderate hepatic impairment were resolved without treatment, except for one AE in a subject who had an increased total bilirubin level until the last follow-up visit, but it was considered probably related to the hepatic impairment condition rather than the investigated drug. The other AEs from the moderate hepatic impairment group were considered possibly related to the investigated drug nemonoxacin, and all 4 AEs from the healthy subjects related to the laboratory test results were considered possibly related to nemonoxacin as well. All the AEs from the 2 groups were resolved without intervention.

Table II. Concomitant medication use in study subjects.

Subject	Concomitant Medication					
	Symptomatic Treatment			Uretic Agent		Antiviral and Uretic Agent
G01	Humulin 70/30	Polyene phosphatidylcholine	Compound amino acid			
G02				Furosemide	Antisterone	Entecavir
G03	Anethole trithione tablets	Metoprolol		Antisterone		
G04	Anethole trithione tablets			Antisterone		Entecavir
G05	Leucogen tablets	Propranolol	Fuzheng Huayu capsule (Chinese traditional medicine for liver dysfunction)	Antisterone		Entecavir
G06				Antisterone	Hydrochlorothiazide	Entecavir
G07	Diammonium glycyrrhizinate	Compound amino acid	Ursodeoxycholic acid			Entecavir
G08	Amlodipine	Potassium chloride sustained-release tablets				Entecavir
G09	Glutathione					Entecavir
G10	Silibinin capsules	Fuzheng Huayu capsule (Chinese traditional medicine for liver dysfunction)		Antisterone		Entecavir
J07	Amlodipine					
J08	Zhenju Jiangya tablets (Chinese traditional medicine for hypertension)					

Table III. Noncompartmental analysis of pharmacokinetic parameters of nemonoxacin in the hepatic impairment group and in the healthy control group. Values are given as mean (SD) [%CV].

Variable	C_{max} (μg/mL)	AUC_{0-24h} (μg · h/mL)	AUC_{0-72h} (μg · h/mL)	$AUC_{0-\infty}$ (μg · h/mL)	$t_{1/2}$ (h)	CL_t/F (L/h)	V_d/F (L)	$MRT_{0-\infty}$ (h)
Hepatic impairment group (n = 10)	8.296 (2.643) [31.9]	49.60 (14.22) [28.7]	58.50 (17.30) [29.6]	58.97 (17.46) [29.6]	10.54 (1.56) [14.8]	9.22 (2.90) [31.5]	141.32 (54.21) [38.4]	11.24 (1.66) [14.7]
Healthy control group (n = 10)	6.870 (1.979) [28.8]	43.43 (9.28) [21.4]	49.74 (10.16) [20.4]	50.15 (10.23) [20.4]	10.42 (1.22) [11.7]	10.41 (2.42) [23.3]	156.77 (40.36) [25.7]	10.50 (1.58) [15.1]
P	0.108	0.207	0.179	0.183	0.863	0.318	0.430	0.376

CL_t/F = total clearance of the drug from plasma; MRT = mean residence time; V_d/F = apparent volume of distribution.

Population PK Model Building

For the population modeling, a total of 20 subjects with 240 plasma sampling points were collected, including 20 predose samples and 220 postdose samples. One plasma concentration collected at 72 h from a healthy subject was higher than the sample collected at 48 h; it was therefore excluded from the model construction. To build a feasible base model, different compartment models were tested. A 2-compartment model was found to be more suitable than a 1-compartment model for fitting the plasma drug concentration. However, it was difficult to fit the plasma points at low drug concentrations using the 2-compartment model. Compared with the 2-compartment model, the 3-compartment model was better, especially in fitting the plasma points at low drug concentrations. Quinolones such as ciprofloxacin are absorbed primarily from the duodenum and jejunum.[17] In addition, some articles have reported that patients with liver cirrhosis have delayed gastric emptying.[18,19] Considering that the absorption of nemonoxacin can be affected by delayed gastric emptying, we conducted the model both with and without the absorption lag time (ALAG) model.

The results showed that the OFV was –266.068 in the model without ALAG, and the OFV in the model with ALAG was decreased by 67.886 to a final value of –333.954 ($P < 0.001$). Finally, the model with ALAG was used. The OFV was –333.954 in the base 3-compartment model. In the base 3-compartment model, the nemonoxacin population PK (popPK) parameters included central compartment clearance (CL/F, 10.1 L/h), central compartment volume (V1/F, 44.8 L), Q2/F (0.782 L/h), V2/F (20.6/L), Q3/F (18 L/h), V3/F (44.2 L), absorption rate constant (2.25 1/h), and ALAG (0.251 h). The interindividual variability and residual variability were well described by the exponential model and the proportional error model. Overall, the 3-compartment model could perfectly fit most of the drug concentrations.

Covariate Analysis

The eta values of Q2/F and Q3/F were fixed as 0, which meant that their interindividual variability was 0. Therefore, the impact of covariates on Q2/F and Q3/F was not tested. In the base model, there was no significant impact of weight on the eta value

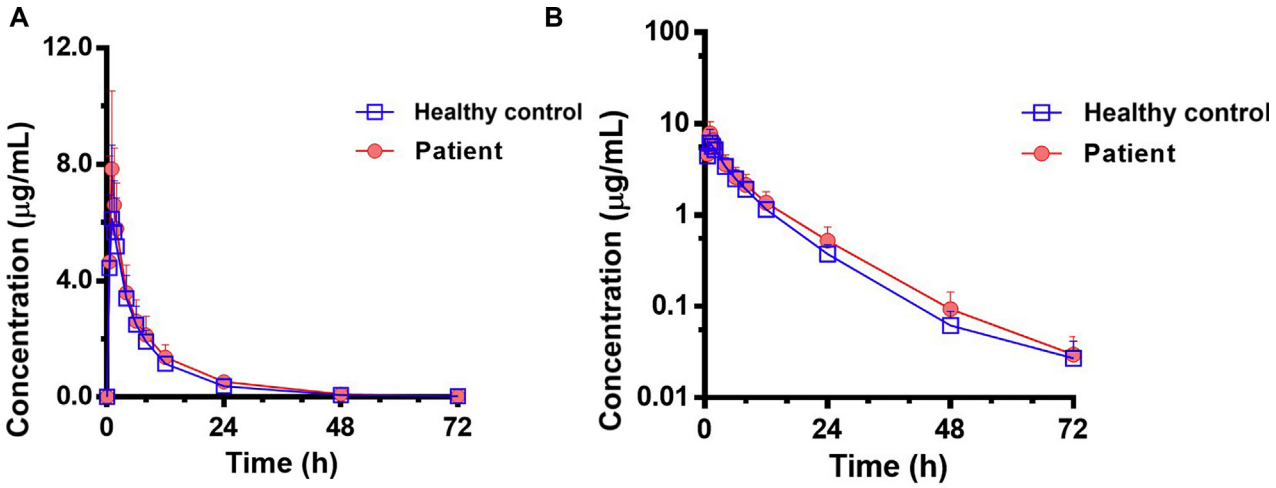

Figure 1. Nemonoxacin concentration versus time curves for the hepatic impairment group and the healthy control group. (A) Normal concentration scale; (B) concentration with a logarithmic scale.

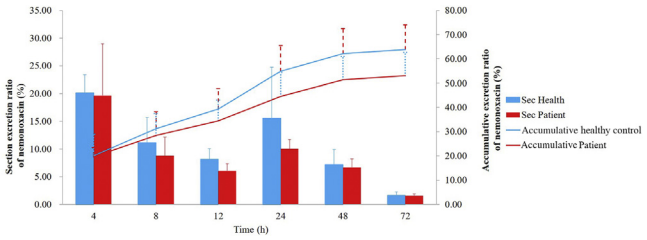

Figure 2. The urine section excretion and accumulative excretion ratios of the moderate hepatic impairment group and the healthy control group.

of V2/F ($P = 0.077$), and thus weight was not included in the stepwise method. Covariate analysis indicated that weight affected CL/F, V1/F, and V3/F and that eGFR only affected CL/F in the power function model, whereas sex affected V3/F in the linear model by forward selection and backward deletion.

The final model was validated by using the nonparametric bootstrap method. The results showed a complete overlap of the 95% CIs, which estimate the ranges of the 2.5th to 97.5th percentiles, indicating that the final model was robust (Table V). The final model indicated strong stability with 868 bootstrap runs that fitted successfully, and the bootstrap estimates displayed results very similar to the population estimates as well. The covariate equations are shown as follows:

$$CL/F = TVCL \times (Weight/70)^{0.75} \times (eGFR/103.5)^{1.34}$$

$$V1/F = TVV1 \times (Weight/70)$$

$$Q2/F = TVQ2$$

$$V2/F = TVV2$$

$$Q3/F = TVQ3$$

$$V3/F = TVV3 \times (Weight/70) \times \theta_{v3sex}$$

Table IV. Number of adverse events in the hepatic impairment group and in the healthy control group.

Adverse Event	Hepatic Impairment Group	Healthy Control Group
Decreased white blood cell count	2	0
Decreased platelet count	1	0
Increased total bilirubin level	2	0
Increased ALT level	1	0
Increased AST level	1	0
Mild T-wave change	1	0
Prolonged QT interval	2	0
Headache	0	1
Ventricular premature beat	0	1
T-wave changes	0	2
Sinus bradycardia	0	1

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

$$\theta_{V3sex} = \begin{cases} 1 & \text{if } V3/F = 1(\text{male}) \\ 0.760 & \text{if } V3/F = 2(\text{female}) \end{cases}$$

The goodness-of-fit values of the individual and population scatter plots show that the final model fit the concentrations very well (Figure 3). The fitting effect of the final model on the points at low drug concentrations was better than that of the base model, and the conditional weighted residuals were more evenly distributed on both sides of the horizontal axis. Figure 4 shows the visual predictive check results using 1000 Monte Carlo simulations. The observed concentration was included in the range of CIs when the median and 95% CI lines were located near the middle area of the 1000 simulation results, demonstrating the sufficiency of the predictive power of the model. Open circles represent the observed concentrations; the solid and the dashed lines represent the median and the 95% CIs of the observation, respectively. The middle red-shaded areas represent the 95% CIs of the median for the results of 1000 simulations in the final model, and the blue-shaded areas represent the 95% CIs of the 2.5th and 97.5th percentiles for the results of 1000 simulations of the final model.

DISCUSSION

Nemonoxacin has a potent antibacterial activity against MSSA (MIC_{90} of $\leq$0.03 mg/L), ciprofloxacin-susceptible MRSA (MIC_{90} of $\leq$0.03 mg/L), community-acquired MRSA (MIC_{90} = 0.06 mg/L), vancomycin-susceptible *Enterococcus faecalis* (MIC_{90} = 0.5 mg/L), *S pneumoniae* (MIC_{90} = 0.06 mg/L), levofloxacin-resistant *S pneumoniae* (MIC_{90} = 1 mg/L), and other *Streptococcus* species (MIC_{90} = 0.12–0.25 mg/L), which often cause respiratory tract infections.[20,21] The PK/pharmacodynamics index of nemonoxacin is calculated using the ratio of $fAUC_{0-24h}$ to MIC, and the target value of nemonoxacin against *S pneumoniae* is 47.05.[22] In the PK study by Guo et al[6] of nemonoxacin involving healthy Chinese subjects, the concentration–time profiles of the 500- and 750-mg doses of nemonoxacin on days 1 and 10 by the multiple-dose study were similar to those of the single-dose study. However, the 90% CI of the AUC_{0-72h} ratio in this study did not cover the range of 80%–125%; therefore, we could not conclude that hepatic impairment does not affect the PK of nemonoxacin.[15] Based on the PK parameters and the PK/pharmacodynamics index in this study as well as previous studies, we recommend that there is no need to consider a dose adjustment of nemonoxacin for patients with mild or moderate hepatic impairment. The administration of nemonoxacin 500 mg for the treatment of CAP in adults with mild or moderate hepatic impairment could also achieve efficacious and safe clinical outcomes as patients with normal hepatic function.

Seven AEs related to ECG abnormalities were reported in this study. Two AEs of QT interval extension occurred in the moderate hepatic impairment group. The AUC_{0-72h} values of the 2 subjects were 65.29 μg h/mL and 42.75 μg h/mL, respectively. In the study by Zhao et al,[23] nemonoxacin was classified as generally safe at the therapeutic dose (500 mg) and potentially dangerous at the supratherapeutic dose (750 mg), but a correlation between Fridericia-corrected QT and the plasma drug concentration of nemonoxacin was not observed. In this study, nemonoxacin was well tolerated in patients with moderate hepatic impairment as well as in healthy subjects. Therefore, the consideration of dose adjustment of nemonoxacin

Table V. Population pharmacokinetic parameters of nemonoxacin and the bootstrap results.

Pharmacokinetic Parameter	Estimated (RSE%)	868 Successful Bootstrap Median (95% CI)
CL/F (L/h)	11.4 (3.3)	11.4 (10.6–12.0)
V1/F (L)	50.4 (9.4)	49.9 (41.6–59.7)
Q2/F (L/h)	0.753 (27.4)	0.782 (0.515–1.200)
V2/F (L)	20.5 (11.7)	21.0 (16.5–26.1)
Q3/F (L/h)	16.3 (24)	16.6 (10.0–23.5)
V3/F (L)	53.3 (8.9)	53.5 (44.5–63.7)
KA (1/h)	2.42 (32.4)	2.47 (1.53–4.93)
ALAG (h)	0.257 (22)	0.270 (0.157–0.366)
$\theta_{CLweight}$	0.75,* FIX	–
$\theta_{V1weight}$	1,† FIX	–
$\theta_{V3weight}$	1,‡ FIX	–
θ_{CLegfr}	1.34,§ (22.5)	1.34 (0.87–2.31)
θ_{V3sex}	–0.240,‖ (24.4)	–0.244 (–0.355 to –0.108)
Interindividual variability		
CL/F, %	13.3 (14.6)	12.8 (8.59–16.1)
V1/F, %	17.9 (28.7)	17.5 (5.8–27.5)
Q2/F, %	0, FIX	–
V2/F, %	56.1 (43.3)	55.0 (18.1–111.5)
Q3/F, %	0, FIX	–
V3/F, %	11.0 (35.6)	10.2 (2.7–17.2)
KA, %	78.2 (20.3)	73.7 (43.7–107.3)
ALAG, %	40.7 (38.6)	36.2 (13.4–72.8)
Residual variability		
Proportional error (%)	11.2 (9.9)	10.8 (8.49–13.1)

ALAG = absorption lag time; CL/F = central compartment clearance; FIX = assume as constant which was not accessed by bootstrap; KA = absorption rate constant; Q2/F = clearance between the central compartment and the deep peripheral compartment; Q3/F = clearance between the central compartment and the shallow peripheral compartment; RSE = residual standard error; V1/F = central compartment volume; V2/F = deep peripheral compartment volume; V3/F = shallow peripheral compartment volume.

* The population parameter of CL/F($\theta_{CLweight}$).[24].

† The population parameter of V1/F($\theta_{V1weight}$t).

‡ The population parameter of V3/F($\theta_{V3weight}$).

§ The population parameter of CL/F(θ_{CLegfr}).

‖ The population parameter of V3/F(θ_{V3sex}) when sex was 1.

for patients with severe hepatic impairment requires further study. It is recommended that patients with severe hepatic impairment who take nemonoxacin are monitored by using an ECG.

During establishment of the base model, it was found that the 2-compartment model (base model) was much better than the 1-compartment model in fitting the plasma drug concentration. However, it was difficult to use the 2-compartment model to fit the points at low drug concentrations in plasma. The 3-compartment model was determined to fit the plasma drug concentration of nemonoxacin, especially at low drug concentrations. The PK parameters calculated by using the 3-compartment model were similar to those calculated by using NCA. The popPK model was validated as well. In the

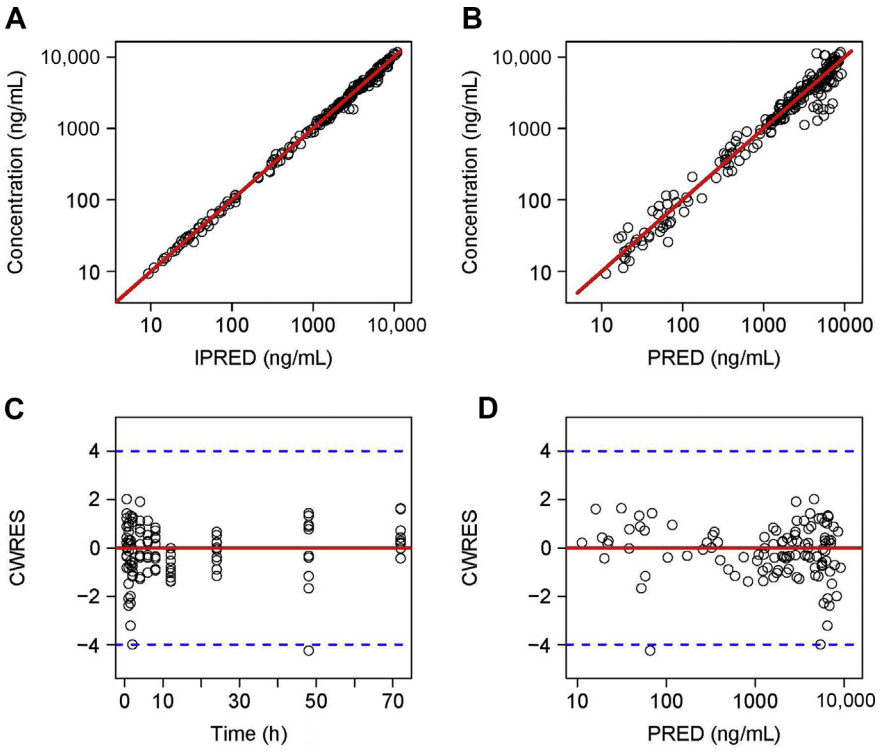

Figure 3. The goodness of fit of the 3-compartment model, the final model. (A) Individual predicted concentration (IPRED) versus the observed concentration. (B) Population-predicted concentration (PRED) versus the observed concentration. (C) Conditional weighted residuals (CWRES) versus time. (D) CWRES versus PRED. The solid line in (A) and (B) represents the regression line; in (C) and (D), the solid line is at the position where the CWRES equals 0.

final model, weight affected CL/F; V1/F, V3/F, and eGFR only affected CL/F in the power model; and sex (male or female) affected V3/F in the linear model. The result that eGFR affected CL/F was probably because nemonoxacin is mainly excreted by the renal pathway.

Based on the final popPK model of nemonoxacin, the hepatic function did not have a significant impact on the PK parameters of nemonoxacin, but renal function was a meaningful covariate that is consistent with its PK characteristics. Meanwhile, the AUC_{0-72h} ratio of the hepatic impairment group to the healthy control group of 3 pairs was >1.25, with values of 2.42, 1.45, and 1.28, respectively. The eGFRs of the subjects in the hepatic impairment group were 88, 96, and 90 mL/min/1.73 m^2; the eGFRs of the subjects in the healthy control group were 118, 112, and 104 mL/min/1.73 m^2. It could also be that renal function is a meaningful covariate for the AUC of nemonoxacin. Thus, there is no need to consider a dose adjustment of nemonoxacin for patients with mild or moderate hepatic impairment. Because renal function could potentially affect the PK parameters based on the popPK model, a dose adjustment of nemonoxacin or intensive monitoring should be considered among patients with renal function impairment.

However, some limitations in this study should also be mentioned. The sample size was small. No PK data of patients with severe hepatic impairment were obtained, and the final popPK model cannot predict the PK parameters of nemonoxacin because hepatic function was not a covariate in the equation, suggesting that the dose adjustment of nemonoxacin in patients with severe hepatic impairment needs

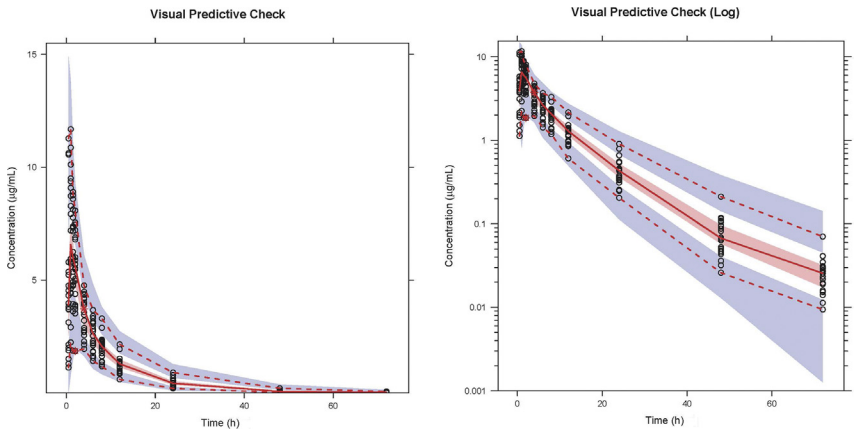

Figure 4. The visual predictive check results validated the predictive ability of the final model. The circles in the figure represent the observed concentrations; the solid line and the dashed lines represent the median and the 95% CIs of the observed concentrations, respectively. The middle red-shaded area represents the 95% CI of the median for the results of 1000 simulations of the final model, and the blue-shaded areas represent the 95% CIs of the 2.5th and 97.5th percentiles for the results of 1000 simulations of the final pharmacokinetic model.

further study. Moreover, due to the lack of PK data among patients with moderate or severe renal impairment, further investigations are necessary to study patients with renal function impairment, which could validate the prediction of the popPK model in the future.

CONCLUSIONS

Overall, based on this study, it is not necessary to consider a dose adjustment of nemonoxacin in patients with mild or moderate liver dysfunction. The 3-compartment model was considered to be the best at fitting the PK parameters of nemonoxacin among all of the compartment models. The CL/F and V/F of nemonoxacin could be affected by the eGFR and the weight of patients, respectively. This PK study showed the efficacy and safety of nemonoxacin in patients with mild or moderate liver dysfunction and provided important guidance for its clinical use in the future.

CONFLICTS OF INTEREST

The authors have indicated that they didn't receive the support from industry or organizations that might have influenced this work and the study sponsor didn't involve in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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Kang contributed to protocol development, trial conduct, formal analysis, popPK model, and manuscript writing. Li contributed to the drug concentration test and formal analysis. Xu and Wang contributed to the popPK model building. Chen contributed to formal analysis. Wu, Guo, and Yu contributed to protocol review and trial conduct. J. Zhang contributed to conceptualization, funding acquisition, and protocol review. Y. Zhang contributed to conceptualization and protocol review. All authors reviewed and approved the article submission.

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