Nemonoxacin Dosage Adjustment in Patients with Severe Renal Impairment Based on Population Pharmacokinetic and Pharmacodynamic Analysis

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Abstract

Aims: To optimize the dosing regimen in patients with severe renal impairment based on population pharmacokinetic/pharmacodynamic (PPK/PD) analysis. Methods: The pharmacokinetics and safety of nemonoxacin was evaluated in a single-dose, open-label, nonrandomized, parallel-group study after single oral dose of 0.5 g nemonoxacin capsule in 10 patients with severe renal impairment and 10 healthy controls. Both blood and urine samples were collected within 48 hours after admission and determined the concentrations. A PPK model was built using nonlinear mixed effects modelling. The probability of target attainment (PTA) and the cumulative fraction of response (CFR) against S. Pneumoniae and S. aureus was calculated by Monte Carlo simulation. Results: The data best fitted to a two-compartment model, from which the PPK parameters were estimated, including clearance (8.55 L/h), central compartment volume (80.8 L), and peripheral compartment volume (50.6 L). The accumulative urinary excretion was 23.4±6.5% in severe renal impairment patients and 66.1±16.8% in healthy controls. PPK/PD modeling and simulation of 4 dosage regimens found that nemonoxacin 0.5 g q48h was the optimal dosing regimen in severe renal impairment patients, evidenced by higher PTA (92.7%) and CFR (>99%) at nemonoxacin MIC [?] 1 mg/L against S. pneumoniae and S. aureus. The alternative regimens (0.25 g q24h; loading dose 0.5 g on Day 1 followed by 0.25 g q24h) were insufficient to cover the pathogens even if MIC [?] 0.5 mg/L. Conclusion: An extended dosing interval (0.5 g q48h) may be appropriate for optimal efficacy of nemonoxacin in case of severe renal impairment.

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Running title: Nemonoxacin Dosage Adjustment in Severe Renal Impairment

Abbreviations:

AE adverse event

AUC Area under curve

BMI body mass index

CFR cumulative fraction of response

CI confidence interval

CL clearance

CL_r renal clearance

CrCl Creatinine clearance

ESRD end-stage renal disease

IIV inter-individual variability

MD maintaining dose

MRSA methicillin-resistant *Staphylococcus aureus*

OFV objective function value

PK/PD pharmacokinetics/pharmacodynamics

PPK population pharmacokinetics

PRSP penicillin-resistant *Streptococcus pneumoniae*

PTA probability of target attainment

TBW total body water

V1 central compartment volume

V2 peripheral compartment volume

VPC visual predictive check

ABSTRACT

Aims: To optimize the dosing regimen in patients with severe renal impairment based on population pharmacokinetic/pharmacodynamic (PPK/PD) analysis.

Methods: The pharmacokinetics and safety of nemonoxacin was evaluated in a single-dose, open-label, nonrandomized, parallel-group study after single oral dose of 0.5 g nemonoxacin capsule in 10 patients with severe renal impairment and 10 healthy controls. Both blood and urine samples were collected within 48 hours after admission and determined the concentrations. A PPK model was built using nonlinear mixed effects modelling. The probability of target attainment (PTA) and the cumulative fraction of response (CFR) against*S. Pneumoniae* and *S. aureus* was calculated by Monte Carlo simulation.

Results: The data best fitted to a two-compartment model, from which the PPK parameters were estimated, including clearance (8.55 L/h), central compartment volume (80.8 L), and peripheral compartment volume (50.6 L). The accumulative urinary excretion was 23.4±6.5% in severe renal impairment patients and 66.1±16.8% in healthy controls. PPK/PD modeling and simulation of 4 dosage regimens found that nemonoxacin 0.5 g q48h was the optimal dosing regimen in severe renal impairment patients, evidenced by higher PTA (92.7%) and CFR (>99%) at nemonoxacin MIC [?] 1 mg/L against *S. pneumoniae* and *S. aureus* . The alternative regimens (0.25 g q24h; loading dose 0.5 g on Day 1 followed by 0.25 g q24h) were insufficient to cover the pathogens even if MIC [?] 0.5 mg/L.

Conclusion: An extended dosing interval (0.5 g q48h) may be appropriate for optimal efficacy of nemonoxacin in case of severe renal impairment.

KEYWORDS

renal impairment; dosage adjustment; nemonoxacin; population pharmacokinetics; *Streptococcus pneumoniae* ; *Staphylococcus aureus* ; pharmacokinetics/pharmacodynamics; community-acquired pneumonia

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Nemonoxacin is one of the latest quinolones used to treat infections caused by susceptible pathogens, especially *S. pneumoniae* and*S. aureus* . Although it is primarily eliminated via kidneys, the pharmacokinetics and safety of nemonoxacin have not been studied in patients with severe renal impairment. PPK/PD analysis is the economic and efficient practice to guide rational drug use based on individual characteristics.

WHAT THIS STUDY ADDS

This study investigated the safety and pharmacokinetics of single doses of nemonoxacin in severe renal impairment patients compared with that in health controls. Creatinine clearance was identified as the main covariate influencing nemonoxacin pharmacokinetics. There is a significant non-renal elimination pathway in renal impairment patients. Model-based simulations showed nemonoxacin 0.5 g q48h might be the optimal regimen in severe renal impairment. These findings should be validated in real patients via clinical studies.

INTRODUCTION

Pneumonia continues to be one of the leading causes of morbidity and mortality worldwide, especially in low-income countries [1,2]. Among patients seeking medical treatment, *Streptococcus pneumoniae* is the most predominant bacterial pathogen, accounting for more than 25% of community-acquired pneumonia (CAP) cases [3,4].*Staphylococcus aureus* is usually associated with more severe CAP cases. Notably, the incidence of serious infections caused by methicillin-resistant *S. aureus* (MRSA), including community-acquired MRSA, is on the rise globally [5]. According to current Infectious Diseases Society of America and American Thoracic Society guidelines, monotherapy with a respiratory fluoroquinolone is strongly recommended for managing CAP in adults [6].

Nemonoxacin, one of the latest broad-spectrum non-fluorinated quinolones, has shown potent bactericidal effect on gram-positive and gram-negative bacteria, as well as atypical pathogens [7]. Nemonoxacin targets

both bacterial DNA gyrase and topoisomerase IV, and as a result, blocks bacterial DNA supercoiling. Compared with its fluorinated analogs, nemonoxacin is more active *in vitro* against MRSA, penicillin-resistant*S. pneumoniae* , ciprofloxacin-resistant MRSA, and levofloxacin-resistant *S. pneumoniae* . Both intravenous and oral dosage forms of nemonoxacin were investigated at the standard dose of 0.5g q24h in phase I to III clinical trials [8]. The clinical outcomes have proved that nemonoxacin is more tolerable and non-inferior to other classic fluoroquinolones such as levofloxacin. At present, the capsule formulation of nemonoxacin has been approved successively in Taiwan and Mainland of China to treat CAP in adults and granted fast track designations by the US Food and Drug Administration [9-11].

Clinical trials have demonstrated the favorable pharmacokinetic (PK) profile of nemonoxacin, such as high oral bioavailability (100%), low plasma protein binding (16%), and minimal drug accumulation. No metabolite or only a minor metabolite (<5%) was observed in metabolism studies of nemonoxacin since the drug was predominantly eliminated via the kidneys in unchanged form [9,12,13]. Therefore, it is reasonable to believe that renal function has direct effect on the systemic clearance (CL) and exposure of nemonoxacin. On the other hand, a recent thorough QT/QTc study revealed that the cardiotoxicity of nemonoxacin increased in a dose-dependent manner. The cardiac repolarization characteristics at therapeutic dose (0.5 g q24h) are acceptable, while supratherapeutic dose (0.75g q24h) should raise more concerns [14]. Therefore, dose adjustment appears necessary for nemonoxacin in patients with renal impairment.

Generally speaking, renal dysfunction probably affects the pharmacodynamic (PD) properties of drugs [15]. The most clinically relevant PK/PD index of nemonoxacin is the area under the plasma concentration-time curve of the free drug over the minimum inhibitory concentration ratio (f $AUC_{0\text{-}24h}$/MIC) [16]. To maximize the probability of attaining the target pharmacodynamic exposure of nemonoxacin against the clinical pathogens of CAP and minimize the risk of exposure-related toxicities, population PK/PD analysis and simulation of dosage adjustment were conducted to find the optimal dosing regimen for treatment of CAP in patients with severe renal impairment.

MATERIALS AND METHODS

This study was conducted in accordance with the principles of Declaration of Helsinki and Good Clinical Practices guidelines. The protocol and amendments were approved by the Huashan Hospital Institutional Review Board, Fudan University, on August 3, 2016 (no. 2016-217). All the eligible subjects enrolled at a single center in China from April 2017 to November 2019 and provided written informed consent prior to any study procedure.

Study Design

This trial was designed as a single-center, open-label, nonrandomized, parallel-group study. Ten healthy subjects with normal renal function, defined by estimated glomerular filtration rate (eGFR) [?] 90 mL/min/, and 10 subjects with severe renal impairment or end-stage renal disease (eGFR [?] 30 mL/min/) received a single oral dose of 0.5 g nemonoxacin capsule. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.

Eligibility Criteria

The main inclusion criteria included male or female volunteers aged 18 to 75 years, body mass index (BMI) of 17-30 kg/m^2. Volunteers agreed to use an acceptable contraception method throughout the study and until one month after the end of study. The nondialysis-dependent patients with severely impaired renal function or ESRD were eligible for enrolment into severe renal impairment group. The healthy controls were matched to the patients with severe renal impairment in terms of age (+-5 years), sex, and BMI (+-15%). A healthy status was determined according to the evaluation of medical history, physical examination, 12-lead ECG, and laboratory tests. Consumption of any caffeine-containing product or xanthine was forbidden from 48 hours predose to the end of treatment period.

The subjects were excluded if they had any of the following: an allergic constitution, known or suspected hypersensitivity to quinolones; positive urine test for drugs or alcohol; smoker; use of any investigational

drug; positive test for hepatitis B surface antigen, hepatitis C virus, human immunodeficiency virus, or syphilis rapid plasma reagin; use of inhibitor or inducer of hepatic cytochrome metabolism enzymes, or other drugs probably affecting the PK profile of nemonoxacin. The subjects with a history of acute or chronic disease, including chronic liver, renal, cardiovascular, neurologic, psychiatric, gastrointestinal, pulmonary, urinary, or endocrine disease, were excluded from healthy control group. Clinically significant abnormal 12-lead ECG and abnormal laboratory test result also precluded subject enrollment. The subjects with sere renal impairment or ESRD were considered clinically stable except the case of moderate or severe anemia (hemoglobin $<$ 60 g/L), severe hypertension (diastolic blood pressure $>$ 110 mmHg or systolic blood pressure $>$ 180 mmHg), diabetic nephropathy, urinary incontinence, anuria, or significant increase of serum creatinine from baseline ([?] 30%).

Assessment

Venous blood samples were collected for analysis of nemonoxacin PK at predose, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, and 72 h postdose. Urine sample was collected at predose and in the following postdose intervals: 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 h.

Safety was evaluated by examining the prevalence and severity of adverse events (AEs), vital signs, laboratory tests (hematology, clinical chemistry, and urinalysis), physical examination, and 12-lead ECG. The final follow-up visit was conducted at 72 h after administration of nemonoxacin.

Bioanalytical Method

The levels of nemonoxacin in plasma and urine were assayed using a validated liquid chromatography-tandem mass spectrometry (ACQUITY UPLC, Waters, USA and 4000 QTRAP, AB Sciex, USA) method modified from previous report [17]. Liquid chromatographic separation was achieved on an ACE UltraCore 2.5 super C18 column (4.6 mm x 50 mm, 2.5 μm, Advanced Chromatography Technologies Ltd, UK) using the mobile phase composed of A (0.3% formic acid aqueous solution) and B (methanol) at a flow rate of 0.6 mL/min. The elution program was 60% phase A, 0–0.3 min; 60% to 30% phase A, 0.3–0.9 min; 30% phase A, 0.9–1.5 min; 30% to 60% phase A, 1.5–1.8 min; and 60% phase A, 1.8–2.0 minutes. The column temperature was 40°C. Nemonoxacin was analyzed using positive multiple reaction monitoring mode and operating in electrospray ionization (ESI) ion source. The ion pairs for quantitative analysis of nemonoxacin and its stable isotope-labeled internal standard (nemonoxacin-d3) were m/z 372.5 - 354.5 andm/z 375.5 - 357.5 at 12 eV collision energy. An aliquot of 50 μL PK sample (plasma or urine) was precipitated by 450 μL acetonitrile. After centrifugation at 3000 × g for 10 min, the supernatant was diluted with 50% methanol/0.1% formic acid aqueous solution in a ratio of 1:1 or 1:40, respectively. The intra- and inter-batch accuracy of nemonoxacin in plasma varied from 98.0% to 104.0% and 100.0% to 101.3% (coefficient of variation [?] 8.6%). Likewise, the intra- and inter-batch accuracy of urine assay varied from 95.5% to 107.5% and 97.2% to 104.2% (coefficient of variation [?] 6.2%). The calibration curves were linear in the range of 0.0500-20.0 μg/mL for plasma (r^2 [?] 0.995) and 2.00-1000 μg/mL for urine (r^2 [?] 0.998).

Population Pharmacokinetics Modeling

The population pharmacokinetic (PPK) profile of nemonoxacin was evaluated using plasma concentration data obtained from the patients with severe renal impairment and healthy controls. A nonlinear mixed-effects model software (NONMEM 7.4, ICON Development Solutions, USA), Modeling and Simulation Studio (Mas Studio 1.2.6 stable, BioVoice & BioGuider Ltd., Shanghai, China) and Perl-speak-NONMEM (PsN, version 5.0.0, Uppsala University, Sweden) were used for PPK analysis and model validation [18]. R (version 3.6.1) and RStudio (1.2.5001) software were used for statistical tests and plotting. The first-order conditional estimation with interaction approach was adopted for model development. The modeling strategy included establishment of the base model and full model development, assessment of final model adequacy, and model predictive performance and validation.

The structural base model was initially fitted using a compartment disposition model based on the PK data. The final base model was selected by the statistical significance between models using goodness-of-fit

plots, the objective function value (OFV), twice the negative log-likelihood (-2LL), and Akaike's information criterion. The inter-individual variabilities for PK parameters were assumed to follow the multiplicative exponential random effects of the form $\vartheta_i = \vartheta \times \epsilon^{\eta_i}$, where ϑ_i is the value of the parameter as predicted for the individual and ϑ is the population typical value of the parameter. The variability of inter-individual random effect η is a normal distribution with N (0, ω^2). The residual error was tested using the constant coefficient of variation model and expressed as $C_{obs} = C_{pred} \times (1 + \epsilon)$, where C_{obs} is the observed value of an individual, C_{pred} is the predicted value, and ϵ is the intra-individual deviation with N (0, σ^2).

The fixed effects were evaluated for statistical significance in a stepwise manner using a stepwise covariate model building procedure. A decrease of 3.84 in the OFV was considered a significant improvement for the forward inclusion step based on Chi-square test ($\alpha < 0.05$). Meanwhile, the full model was subjected to a backward elimination step with a significance level of $\alpha = 0.01$. The potential covariates of PPK parameters were screened. Age, sex, body weight, BMI, total body water (TBW), eGFR, creatinine clearance (CrCl), and albumin were treated as candidate variables. TBW was obtained using the classic Watson formula (for males, TBW = 2.447 - 0.09156 × age + 0.1074 × height + 0.3362 × weight; for females, TBW = -2.097 + 0.1069 × height + 0.2466 × weight), where age is in years, height in centimeters, weight in kilograms, and water in liters [19,20].

The final PPK model was validated by diagnostic plots and visual predictive check (VPC) techniques comprising 1000 simulations. The median, upper and lower bounds of the 95% prediction interval for PK profiles were compared against the observed plasma concentrations. The nominal 95% confidence intervals (CIs) around the point estimates were generated from 1000 bootstrap samples.

Dosing Regimen Selection and Simulated Datasets

To avoid nemonoxacin accumulation in the patients with impaired kidney function, the standard dosage (0.5 g q24h) should be adjusted by reducing the maintenance dose and/or prolonging the dosing interval. Four dosing regimens (0.25 g q24h, loading dose of 0.5 g on Day 1 followed by maintenance dose (MD) of 0.25 g q24h, 0.5 g q24h, and 0.5 g q48h) of nemonoxacin were compared in 1000 virtual subjects simulated from the final PPK parameters using the original dataset. Descriptive statistics (arithmetic mean, geometric mean, and variation) of the peak levels and $AUC_{0\text{-}24h}$ of nemonoxacin were obtained accordingly for PK/PD analysis.

Monte Carlo Simulation and PK/PD Analysis

S. pneumoniae and *S. aureus* are among the most common CAP pathogens. The MIC distribution was excerpted from Wu's study [21]. The MICs were determined using broth microdilution method according to the recommendation of Clinical and Laboratory Standards Institute. The MIC data used for cumulative fraction of response (CFR) analysis were based on discrete distribution according to the fractions of the isolates at each MIC category. $AUC_{0\text{-}24h}$ was generated based on logarithmic normal distribution to account for the variability in PK parameters. The PK/PD target was $f\ AUC_{0\text{-}24h}/MIC = 47.05$, where f indicates the free fraction of nemonoxacin (0.84). The CFR and the probability of target attainment (PTA) was calculated for four different dosing regimens of nemonoxacin. A dosage regimen was considered optimal if both PTA and CFR are greater than 90%. The simulation was performed on the data from simulated patients with Matlab software (R2018b, MathWorks, Inc., USA).

RESULTS

Study Demographics

In the present study, 20 subjects with or without renal impairment were enrolled. The participants, involving 14 males and 6 females, were characterized by a wide range of ages (26–70 years) and body weights (48.7–84.0 kg) (Table 1). The mean eGFR was 16.8 ± 6.0 ml/min/1.73 m^2 in the renal impairment group (n = 10) and 107.3 ± 11.1 ml/min/1.73 m^2 in the healthy control group (n = 10). Ten patients with severe renal impairment and two healthy subjects reported concomitant medications during follow-up period. The

three most frequently used concomitant medications were amlodipine, sodium bicarbonate, and compound α-ketoacid tablets.

Safety and Tolerability

No serious adverse events (SAEs) were reported. In the renal impairment group, eight subjects experienced 11 AEs, which were mild in severity. Three AEs, including a skin pruritus, an increased serum creatinine level, and a prolonged QT interval, possibly related to study treatment in three (3/10, 30%) renal impairment patients, were resolved on the same day without any intervention. Three AEs from the healthy subjects, which were considered not related to the study drug, were mild in severity and tended to be transient. No clinically relevant change in the physical examination was observed. In general, nemonoxacin was well tolerated in both the renal impairment group and healthy control group (Table 2).

Model Development and Assessment

The PPK model was constructed based on the dataset composed of 240 serial plasma samples. A two-compartment model with linear elimination and first-order absorption provided the most robust fit for nemonoxacin PK profiles. The base model was finally adjusted to account for the effects of delayed gastric emptying by introducing absorption lag time (ALAG) according to a recent study [13]. The inter-individual variability (IIV) for ALAG was excluded from the model as it is too short to be estimated appropriately. Before the inclusion of any covariates, the IIV in the base model parameters was moderate, 39.6% for CL, 18.7% for central compartment volume (V1), and 22.8% for peripheral compartment volume (V2).

The full PK model simultaneously included the covariates possibly affecting PK variability in the building process. The effect of CrCl on CL was found to be the most significant (ΔOFV = -40.471, compared with the base model). The effects of age on CL (ΔOFV = -7.027, P<0.01) and TBW on V1 (ΔOFV = -7.309, P<0.01) were significant in the objective function. These statistically significant covariates were retained in the final model. However, other clinical indicators such as sex, body weight, BMI, eGFR, and albumin were eliminated due to the nonsignificant contribution to ΔOFV or severe multicollinearity between variables. The full PK model successfully converged with an acceptable condition number 386 (the ratio of the largest eigenvalue of the correlation matrix to the smallest one), indicating that the model was stable and not ill-conditioned. The model equations for CL and V1 are presented below:

$$\mathrm{CL} = \left(\frac{\mathrm{age}}{45.5}\right)^{0.326} \times \left(\frac{\mathrm{CrCl}}{57.45}\right)^{0.443} \times \mathrm{TVCL} \times e^{\eta_1}$$

$$\mathrm{V1} = \left(\frac{\mathrm{TBW}}{37.25}\right)^{0.672} \times \mathrm{TVV1} \times e^{\eta_2}$$

where TVCL and TVV1 are the population mean values for CL and V1, respectively. The IIV of CL (η_1) was reduced from 39.6% to 11.3% after including the covariates, while the IIV of V1 (η_2) was declined from 18.7% to 14.5%. All PK parameters demonstrated acceptable precision, with relative standard error (RSE) < 25%. The η-shrinkage was obtained with a fairly small scatter, 3.2% for CL, 11.2% for V1, and 18.3% for V2. The parameter estimates of the full model were presented in Table 3.

Figure 1 presents the full model's diagnostics, which confirmed satisfactory goodness-of-fit between the observed and predicted concentration values. The figure also illustrated conditional weighted residuals (CWRDES) against predicted concentration and time postdose. There were equally spread residuals around the horizontal line without showing any peculiar trends, indicating a reasonable fit to the data. To evaluate the model stability and confidence intervals of the final parameter estimates, VPC and bootstrapping approaches were used. VPC was shown in Figure 2 by plotting the median and 90% prediction intervals which were consistent with the observed plasma concentration data. The original datasets were overlapped with the 95% CIs from 1000 bootstrapping analysis runs and were closely similar to median values, proving that the final model was stable (Table 3).

Simulation and PK/PD Analysis

Simulations were performed on four different multiple-dose regimens of nemonoxacin (0.25 g q24h; loading

dose 0.5 g on Day 1 followed by maintenance dose 0.25 g q24h; 0.5 g q24h; and 0.5 g q48h) to evaluate the effect of renal impairment on PK/PD at steady state. The daily AUCs simulated from 1000 subjects were highly dependent on CrCl. The predicted geometric mean ratio of $AUS_{0\text{-}24h\ ss}$ and 90% CI between the renal impairment and control groups were 2.08 (2.06, 2.11), suggesting a lower dosage requirement (Table 4). The exposure*in vivo* , i.e., daily AUCs of nemonoxacin, of the three adjusted dosing regimens (0.25 g q24h, loading dose 0.5 g followed by maintenance dose 0.25 g q24h, and 0.5 g q48h) in patients with severe renal impairment was similar to that of the standard dosing regimen of nemonoxacin (0.5 g q24h) in subjects with normal renal function (Figure 3). All the three regimens of oral nemonoxacin capsule (0.25 g q24h; loading dose 0.5 g followed by maintenance dose 0.25 g q24h; and 0.5 g q48h) achieved satisfactory PTA of 99.1% - 100% for$f$ $AUC_{0\text{-}24h}$/MIC target (47.05) at MIC [?] 0.5 mg/L against *S. pneumoniae* and *S. aureus* in renal impairment group (Table 5). However, only 0.5 g q48h regimen achieved 92.7% PTA and >99% CFR when MIC [?]1 mg/L. Nemonoxacin 0.25 g q24h or loading-dose strategy led to a grossly inadequate PTA ([?] 17.0% at MIC = 1 mg/L). These findings suggest that clinical efficacy could be expected in an extended-interval dosing strategy (Figure 4).

Urinary Excretion

The excretion of nemonoxacin was described by urinary recovery with the equation below:

$$\text{Recovery} = \frac{\sum (C_{\text{drug, i}} \times V_{\text{urine, i}})}{\text{Dose}}$$

where the recovery was calculated by the sum of multiplying concentration ($C_{\ Drug,\ i}$) and urine volume ($V_{\ Urine\ ,\ i}$) in each collection interval divided by *Dose* . The accumulative excretion of nemonoxacin was 23.4±6.5% in renal impairment group and 66.1±16.8% in healthy controls (Figure 5). The renal clearance (CL_r) of nemonoxacin was 1.31±0.39 L/h in renal impairment group and 7.13±1.92 L/h in healthy controls, which was calculated as$\sum (C_{\text{drug, i}} \times V_{\text{urine, i}})$/AUC over 72 hours.

DISCUSSION

Renal excretion is the major elimination route of nemonoxacin. An important part of the clinical development is investigating the effects of renal impairment on the safety and PK profile to determine the need for dosage adjustment. In the present study, we developed a PPK model of nemonoxacin in 20 subjects with or without renal impairment to evaluate the probability of PK/PD target attainment by MIC and CFR. An optimal dosage regimen was consequently proposed through PK/PD analysis for patients with severe renal impairment. To our knowledge, this is the first clinical trial in compliance with good clinical practice guidelines to investigate the effect of renal function on nemonoxacin dosage.

The covariates in the final PK model were CrCl, age on CL, and TBW on V1. The IIV was 11.3% for CL and 14.5% for V1. The inclusion of these covariates explained 71% (approximately 65% from CrCl) and 22% of the variation in CL and V1, respectively. CrCl level was the most notable source of variability influencing CL. Compared with CrCl, age was regarded as a relatively minor factor for CL. It was concluded from the final model that the CL of nemonoxacin would be reduced by 50% when CrCl decreased by 80%. This is consistent with the PK property of nemonoxacin, i.e., mostly excreted in unchanged form via kidneys [9,11,13]. The urinary excretion study found that the renal elimination of nemonoxacin in unchanged form in healthy subjects (about 66% of the dose) was nearly triple the value in patients with severe renal impairment (about 23% of the dose). It is evident that there is a significant non-renal elimination pathway in renal impairment patients. Several *in vitro* and *in vivo* studies have investigated the mass balance and identify the major metabolite of nemonoxacin [22,23]. Although the fecal excretion was proved to be a minor pathway in healthy volunteers, the increased drug exposure and prolonged elimination half-life in the renal impairment population would probably lead to enhanced biliary and fecal elimination rates [22]. On the other hand, nemonoxacin acyl-β -D-glucuronide, a potential major phase II metabolite, was speculated to be more efficiently biotransformed with the up-regulation of UDP-glucuronosyltransferase pathways [23]. Thus, further study should be conducted to understand the details of nemonoxacin elimination routes and metabolic pathways in renal impairment patients. The PPK analysis also implied that TBW accounted for some IIV in V1. TBW was determined routinely in chronic peritoneal dialysis patients to estimate the volume of urea

distribution, which was calculated by the Watson formula based on combinations of height, weight, gender, and age. Moreover, it is recommended as one of the strongest prognostic variables for assessing patients' body composition or nutritional status and therefore included in the final model.

It would be necessary to consider reduction of nemonoxacin dose in case of more than two-fold increase of steady-state AUC. However, an improved understanding of the PK/PD characteristics of nemonoxacin in the renal impairment population is the key to maximizing its bactericidal activity and minimizing the safety risk. The information is also important for optimization of dosing regimens. *S. pneumoniae* and *S. aureus* , the most common pathogens of CAP, are generally treated with fluoroquinolones and penicillins. Nemonoxacin is a concentration-dependent antibiotic. It has been approved for treatment of CAP in adults. Reportedly, the target value for the most clinically relevant PK/PD index (f $AUC_{0\text{-}24h}$/MIC) of nemonoxacin is 47.05 [16]. The MIC values of nemonoxacin against common target pathogens ranged from 0.015 to 1 mg/L. Monte Carlo simulation showed that only the dosing regimen of nemonoxacin capsule 0.5 g q48h achieved 92.7% PTA and >99% CFR at MIC [?] 1 mg/L in patients with severe renal impairment. A marked decrease was observed both in the C_{max} and PTA at MIC = 1 mg/L for 0.25 g q24h regimen. Therefore, nemonoxacin 0.5 g q48h is recommended for treatment of *S. pneumoniae* and *S. aureus* infections in patients with severe renal impairment. This dosage regimen corresponds to nemonoxacin 0.5 g q24h for CAP patients with normal renal function, guaranteeing excellent clinical efficacy.

All AEs were mild in severity and resolved spontaneously without treatment. No significant difference was observed in the total number of drug-related AEs between the two patient groups, indicating well tolerability in renal impairment patients. However, the incidence of nemonoxacin cardiotoxicity, especially at higher dose (0.75 g q24h), seems to increase in a dose-dependent manner [14]. Compared with the standard dosage (0.5 g q24h), the dosing regimen (0.5g q48h) is unlikely to increase the risk of cardiotoxicity in renal impairment patients. Nevertheless, it is necessary to monitor the adverse drug reactions of nemonoxacin since the AE data were obtained from limited number of subjects in a single-dose, open-label study.

In summary, a PPK model for nemonoxacin is built using the PK data from healthy subjects and severe renal impairment patients. Monte Carlo simulation and PK/PD analysis indicates that nemonoxacin 0.5 g q48h is the optimal dosing regimen in severe renal impairment patients, evidenced by excellent PTA (92.7%) and CFR (>99%) at nemonoxacin MIC [?] 1 mg/L against *S. pneumoniae* and *S. aureus* .

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CONFLICTS OF INTEREST

All other authors declare no conflicts of interest.

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Table 1. Demographic characteristics of the subjects in patients with severe renal impairment and healthy controls

Characteristic	**Severe renal impairment**	**Healthy controls**
Sex, no. Male/Female	7/3	7/3
Age, years Median (range)	45.0 (26.3-70.1)	47.1 (28.2-68.4)
Body weight, kg Mean (SD)	65.5 (12.1)	63.3 (7.7)
BMI, kg/m^2 Mean (SD)	23.8 (3.4)	23.8 (2.3)
CrCl, mL/min Mean (SD)	21.2 (5.9)	106.3 (20.9)
eGFR, mL/min/1.73m^2 Mean (SD)	16.8 (6.0) Stages 4, 5 (<30)	107.3 (11.1) stages 1 (>90)
CKD classification		

BMI: body mass index; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; SD: standard deviation.

Table 2. Adverse events in patients with severe renal impairment and healthy controls after administration of nemonoxacin

Adverse event	**No. of subjects (%)/No. of events**	**No. of subjects (%)/No. of events**
	Severe RI (n = 10)	**Healthy controls (n = 10)**
Any AE	8 (80)/11	2 (20%)/3
Prolonged QT interval	1 (10)	0
Urinary tract infection	2 (20)	0
Skin pruritus	1 (10)	0
Backache	1 (10)	0
Diarrhea	2 (20)	0
Increased Scr	2 (20)	0
Increased serum potassium	1 (10)	0
Increased CPK	1 (10)	0
Increased UA	0	1 (10)
Decreased INR	0	1 (10)
Shortened PT	0	1 (10)

AE: adverse event; RI: renal impairment; Scr: serum creatinine; CPK: serum creatine phosphokinase; UA: urine acid; INR: international normalized ratio; PT: prothrombin time.

Table 3. Parameter estimates and 1000 bootstrap runs from the final model of nemonoxacin

Parameter	**Final model**	**Final model**	**Final model**	
	Estimate	**RSE (%)**	**IIV (%)**	
CL (L/h)	8.55	2.9	11.3	
V1 (L)	80.8	4.5	14.5	
V2 (L)	50.6	8.4	21.3	
KA (1/h)	4.18	22.7	86.7	
Q (L/h)	7.27	15.1	0, FIX	
ALAG (h)	0.316	14.7	31.2	
$\vartheta_{\text{CLage}}{}^{*}$	0.326	31.5	–	
$\vartheta_{\text{CLCrCl}}{}^{\#}$	0.443	8.2	–	
$\vartheta_{\text{V1TBW}}{}^{+}$	0.672	33.7	–	
Residual variability	**Residual variability**	**Residual variability**	**Residual variability**	**Residual variability**
Proportional error	12.0%			

CL: central compartment clearance; V1: central compartment volume; V2: peripheral compartment volume; KA: absorption rate constant; Q: intercompartmental clearance; ALAG: absorption lag time; FIX: assume as constant; RSE: relative standard error; IIV: interindividual variability.

* age effect on CL

CrCl effect on CL

+ TBW effect on V1

Table 4. Daily AUCs of nemonoxacin at steady state from simulated patients

Dosing regimen	$\mathbf{A\Upsilon\hat{}_{0\text{-}24\eta\ \sigma\varsigma}\ (\mu\gamma\cdot\eta/\mu\Lambda)}$	$\mathbf{A\Upsilon\hat{}_{0\text{-}24\eta\ \sigma\varsigma}\ (\mu\gamma\cdot\eta/\mu\Lambda)}$	$\mathbf{A\Upsilon\hat{}_{0\text{-}24\eta\ \sigma\varsigma}\ (\mu\gamma\cdot\eta/\mu\Lambda)}$
	Severe renal impairment	**Normal renal function**	**Ratio***
0.5 g q24h	94.4 (93.5 – 95.2)	45.3 (45.0 – 45.6)	2.08 (2.06 – 2.11)
0.5 g q48h	69.7 (69.2 –70.2)	–	1.54 (1.52 – 1.55)
0.25 g q24h	47.0 (46.6 – 47.5)		1.04 (1.03 – 1.05)
LD: 0.5 g MD: 0.25 g q24h	47.0 (46.6 – 47.4)		1.04 (1.03 – 1.05)

LD: loading dose; MD: maintaining dose.

Data represent genomic mean and 90% prediction intervals (n = 1000).

* Comparison of exposures at steady-state ($AUC_{0\text{-}24h}$) between renal impairment and normal renal function control groups administered at the standard dose (0.5 g q24h).

Table 5. The cumulative fraction of response of nemonoxacin against *S. pneumoniae* and *S. aureus* in community-acquired pneumonia patients with normal renal function or severe renal impairment after selective dose adjustment

Bacteria	**Dosing regimen**	**CFR (%)**	**CFR (%)**
		Severe renal impairment	**Normal renal function**
S. pneumoniae			
	0.5 g q24h	99.3	93.4
	0.5 g q48h	99.9	–

Bacteria	**Dosing regimen**	**CFR (%)**	**CFR (%)**
	0.25 g q24h	94.6	
	LD: 0.5 g MD: 0.25 g q24h	94.2	
S. aureus			
	0.5 g q24h	99.8	98.1
	0.5 g q48h	99.9	–
	0.25 g q24h	98.2	
	LD: 0.5 g MD: 0.25 g q24h	98.0	

CFR: Cumulative fraction of response; LD: loading dose; MD: maintaining dose.

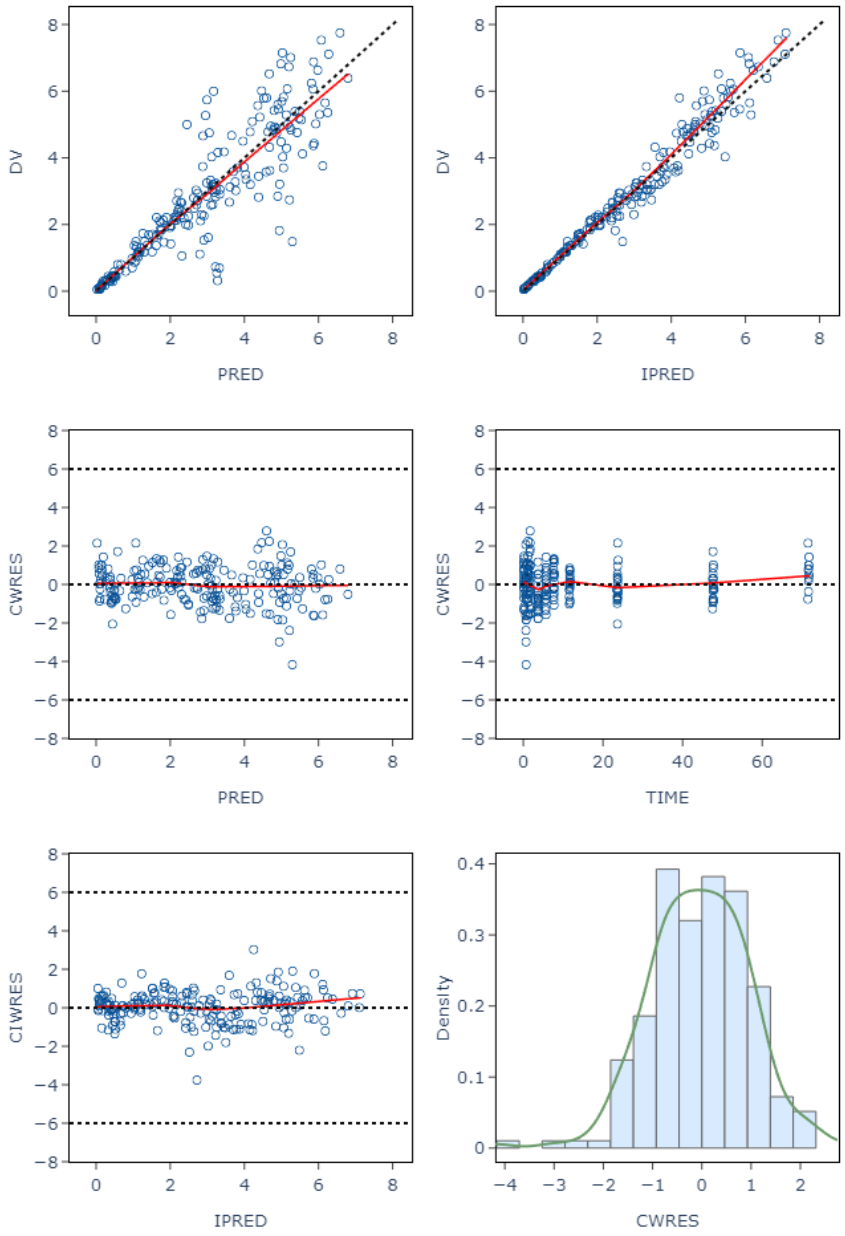

Figure 1. Diagnostic plots for the final population pharmacokinetics model. DV: dependent variable, observed concentrations; PRED: population predicted concentrations; IPRED: individual predicted concentrations; CWRES: conditional weighted residuals; CIWRES: conditional individual weighted residuals; TIME: time after dose in hours

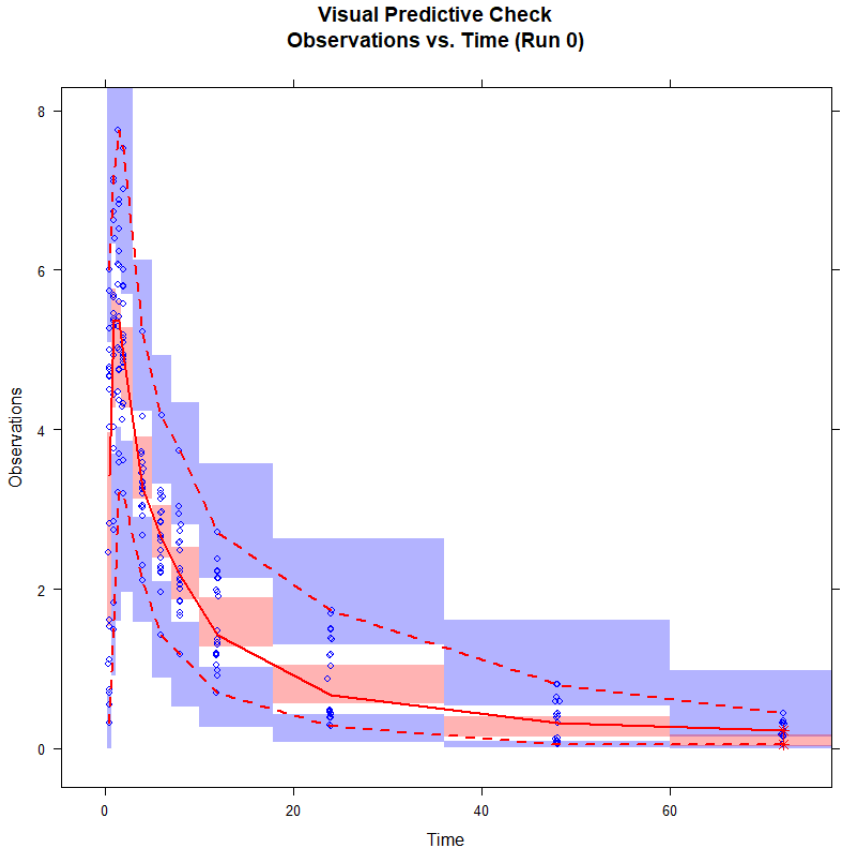

Figure 2. Visual predictive check (VPC) of nemonoxacin for the final model. Observed concentrations were plotted using the blue circle (*), and censored concentrations were plotted using star (*). The shaded area represents the 90% prediction interval and the predicted median of the 10^{th}, 50^{th} and 90^{th} percentiles of simulated data (n = 1000). The lines represent the 10^{th}, 50^{th} and 90^{th} percentiles of observed concentrations.

Figure 3. Comparison of simulated daily AUC (n = 1000) of nemonoxacin between normal renal function control and renal impairment groups treated with different multiple-dose regimens. The shaded area represents the 1/2 ~ 2 times of the AUC/AUC ratio interval. The data in the right panel represent geometric mean and 90% CI.

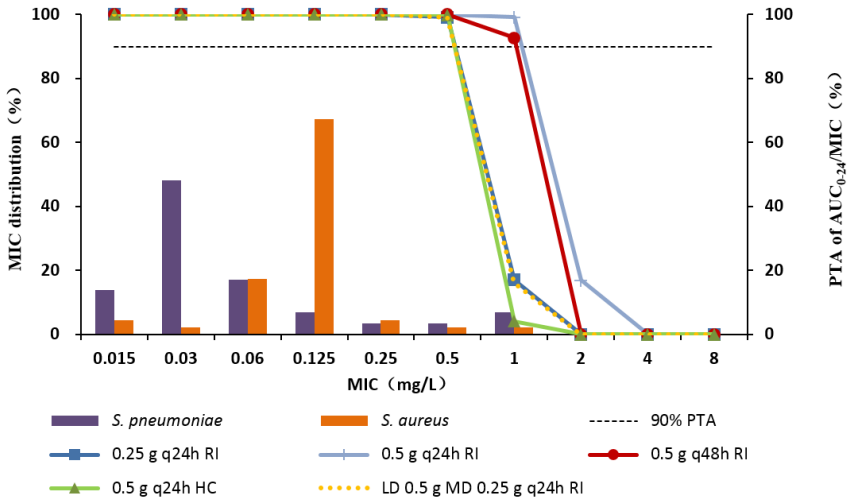

Figure 4. Probability of target attainment (PTA) ($f\mathrm{AUC}_{0\text{-}24\mathrm{h}}/\mathrm{MIC} = 47.05$) in simulated patients with normal renal function or severe renal impairment after selective dose adjustment of nemonoxacin. RI: renal impairment; HC: healthy control; LD: loading dose; MD: maintaining dose.**Figure 5.** Cumulative urine excretion profile in severe patients with renal impairment and healthy controls following single oral administration of nemonoxacin capsule (0.5 g). Data represent mean ± standard deviation.