

Pharmacokinetic study of garenoxacin in severe renal failure patients

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Garenoxacin is a type of fluoroquinolone antibacterial agents. Previous studies have suggested that garenoxacin 400 mg once daily dose is appropriate for patients with normal to moderate renal dysfunction against common bacteria of respiratory infections. However, limited information has been obtained in terms of treatment for severe renal failure patients, such as hemodialysis patients, with this drug. Twenty severe renal failure patients with respiratory infection received single garenoxacin dose (200 mg and 400 mg). By measuring blood concentration of garenoxacin, pharmacodynamics parameters, such as the peak plasma concentration (C_{\max}) and the area under the concentration curve (AUC), were calculated with NONMEM[®]. After single dose of garenoxacin, C_{\max} at the 200 and 400 mg doses were within the range of 2.9 ± 0.6 and $6.0 \pm 1.0 \mu\text{g/mL}$, respectively. The corresponding values for AUC at the 200 and 400 mg doses were within the ranges of 62.3 ± 11.9 and $128.0 \pm 12.5 \mu\text{g} \cdot \text{hr/mL}$, respectively. The mean half-life ($T_{1/2}$) for garenoxacin appeared to be independent of dose (13.9 ± 2.2 hr and 13.7 ± 1.9 hr at the 200 and 400 mg dose). There were no serious adverse events suspected to be related with garenoxacin. Consequently, for severe renal failure patients, the 400 mg once daily garenoxacin dose was expected to be effective against common bacteria of respiratory infections.

Introduction

Garenoxacin, is a type of fluoroquinolone antibacterial agents, has been shown to be effective *in vitro* against a wide range of clinically important Gram-positive and Gram-negative aerobes and anaerobes including some multidrug-resistant pathogen, such as *Streptococcus pneumoniae*, β -lactamase-producing *Moraxella catarrhalis* and ampicillin-resistant *Haemophilus influenzae* (BLNAR)^{1~8}. This antibacterial agent is approved for the treatment of pneumonia, secondary infection of chronic respiratory disease, acute bronchitis, sinusitis, otitis media, laryngopharyngitis and tonsillitis in Japan.

Several studies have revealed that oral dose of garenoxacin is completely absorbed and its pharmacokinetics (PK) is proportional to dose^{9~11}. Additionally, renal clearance of garenoxacin is the major elimination pathway for patients with normal renal function, while excretion of garenoxacin involves non-renal pathways due to metabolism via phase two enzymes^{9, 12, 13}. Accordingly, relevant decrease in total body clearance of garenoxacin is expected in patients with impaired renal function.

In terms of the antibacterial action of fluoroquinolones, a number of recent studies have clearly shown that the area under the concentration-time curve (AUC) divided by the minimum inhibitory concentration (MIC) (AUC/MIC ratio) is the most important predictive value of clinical and microbiological response^{14, 15}. Previous studies have suggested that garenoxacin 400mg once daily dose is appropriate for patients with normal to moderate renal dysfunction from the pharmacokinetics-pharmacodynamics (PK-PD) stand point^{9, 13, 16}.

However, few studies exist on the PK profile of garenoxacin in infected patients with end-stage renal disease. Hence, we investigated the PK of garenoxacin to understand safety and efficacy of the treatment for severe renal failure patients with respiratory infection.

Material and Methods

Subjects

This randomized, open-label, single-dose study was conducted at Aichi Medical University hospital in Aichi Japan. All patients were diagnosed as respiratory infection and had been on a regular thrice-weekly 4hr hemodialysis regimen (blood and dialysate flow rates were fixed at 200 and 500mL/min, respectively). All patients were required to give informed, written consent prior to the initiation of any study-specific procedures, this study was performed in accordance with protocol reviewed and approved by local institution committee.

Any of the following excluded a patient from the study: a history of a serious hypersensitivity reaction to any fluoroquinolones and abnormal electrocardiographic, current clinically significant hepatic disease (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST])

and/or total bilirubin levels greater than or equal to three times the upper limit of normal), malabsorption syndromes or other gastrointestinal disturbances affecting drug absorption, and pregnancy and/or breast feeding.

Dosing procedures

Each subject was given single oral garenoxacin dose of either 200 or 400 mg in non-hemodialysis day. Patients randomized to 200 mg and 400 mg regimen of garenoxacin. The patients were required to fast (nothing to eat or drink except water) for at least 2 hr prior to 2 hr after dose and were prohibited from receiving cation-containing compounds.

Sample collection and assay

Two to four blood samples for measurement of garenoxacin concentrations were taken (around 2 hr and 24 hr after dose). The blood samples were collected into vials containing EDTA as an anticoagulant and were centrifuged to obtain plasma. Plasma samples were stored at -80°C prior to subsequent analysis.

The plasma concentration of garenoxacin was determined by high-performance liquid chromatography (HPLC) (LC-20AD pump, SIL-20A auto-sampler, CTO-20A column oven, DGU-20A3 degasser, CBM-20A system controller, SHIMADZU, Kyoto, Japan) according to the method previously published¹²⁾. In brief, the compound was processed by solid extraction method (Oasis HLB, Waters), then injected on to the column (Develosil ODS-HG-5, 4.6 mm I.D. \times 15 cm, nomura science). The isocratic mobile phase consisted of acetonitrile, citrate buffer solution (pH 3.5), and distilled water (280:150:570, v/v/v). The flow rate was set to 1.0 mL/min, and the detection wavelength was 280 nm. The limits of quantification based on garenoxacin standard curves ranged from 0.03 to 10 $\mu\text{g/mL}$, with the coefficient for each calibration curve was >0.999 . The intra- and inter-day coefficients of variation (%CV) were 0.6 to 9.7% for plasma sample.

Calculation of pharmacokinetic parameters

Analyses are performed the first order conditional estimation with interaction (FOCE-I) algorithm using by using NONMEM[®] software (version VI, double precision, level 1.0)¹⁷⁾.

These parameters; clearance (CL), volume of distribution (Vd) and first-order absorption rate constant (K_a) were calculated by Bayesian estimation ('MAXEVAL=0' and 'Posthoc' in the \$ESTIMATION step) using current concentrations and previously reported model¹³⁾. This model included creatinine clearance (C_{cr}), was fixed 5 mL/min¹⁸⁾, and serum creatinine (S_{cr}) which was assessed at screening conducted within a week prior to garenoxacin dose, and body weight (WT) as variation factors of CL, and WT and gender as Vd. In addition, the area under the curve (AUC), peak plasma concentration (C_{max}), elimination rate constant (K_e) and half-life ($T_{1/2}$) were calculated based on an open one-compartment model.

Safety

The evaluation of drug safety included a review of treatment-emergent clinical adverse events, clinical laboratory findings, and vital signs. Treatment-emergent clinical adverse events were defined as illness, signs, or symptoms, independent of causality, which appeared or worsened after garenoxacin dose. Laboratory adverse events were defined as results deemed clinically significant by the investigator.

Statistical analysis

Statistical analysis was performed using JMP software (version 10; SAS Institute). The univariate relation between each independent variable and garenoxacin dosage was evaluated using a *t* test for continuous variables. Pearson's χ^2 test for categorical variables was used to analyze categorized variables. Significance was defined as $p < 0.05$.

Results

Subject demographics and baseline characteristics

Twenty subjects were enrolled and completed the study (Table 1). Ten patients were received single 200 mg of garenoxacin dose and other 10 patients were received single 400 mg of garenoxacin dose. All subjects' age ranged from 35 to 82 years, with an average of 68 years; their weights ranged from 37.0 to 91.0 kg, with an average of 56.4 kg; 60% ($n=12$) were men and 40% ($n=8$) were women. Based on the data of serum creatinine ranged from 3.46 to 13.50 mg/dL with the average 8.55 mg/dL. The demographic characteristics of the patients were similar across the different dosage groups. All subjects were evaluable for PK and safety analysis, with no subjects withdrawing from the study for any reason.

Pharmacokinetics

Observed garenoxacin concentrations versus the time following an oral dose of 200 and 400 mg, were presented in Figure 1. The final data consisted of 60 plasma garenoxacin concentra-

Table 1. Background of patients enrolled in the study

	Mean \pm SD [Min – Max]				<i>p</i> value
	200 mg		400 mg		
Gender (Male/Female)	5/5		7/3		0.36
Age (y)	69 \pm 10	[46 – 82]	67 \pm 15	[35 – 81]	0.75
Body weight (kg)	59.5 \pm 15.6	[40.0 – 91.0]	53.3 \pm 11.4	[37.0 – 71.0]	0.33
Serum creatinine (mg/dL)	8.76 \pm 2.86	[4.03 – 13.50]	8.34 \pm 2.81	[3.46 – 12.75]	0.74

Pearson's χ^2 test for categorical variables was used to analyze categorized variables. The *t* test was used to analyze continuous variables.

Fig. 1. Observed garenoxacin concentrations versus the time since administration of the single dose of 200 mg (1A) and 400 mg (1B) of garenoxacin
Plotted symbols show the observed concentration data, and the line shows the results of visual predictive checks.

Fig. 1A

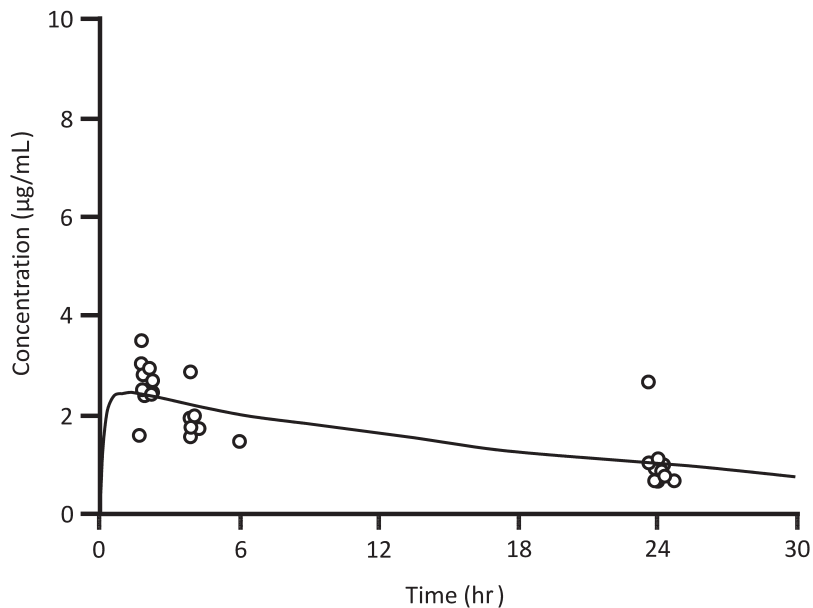


Fig. 1B

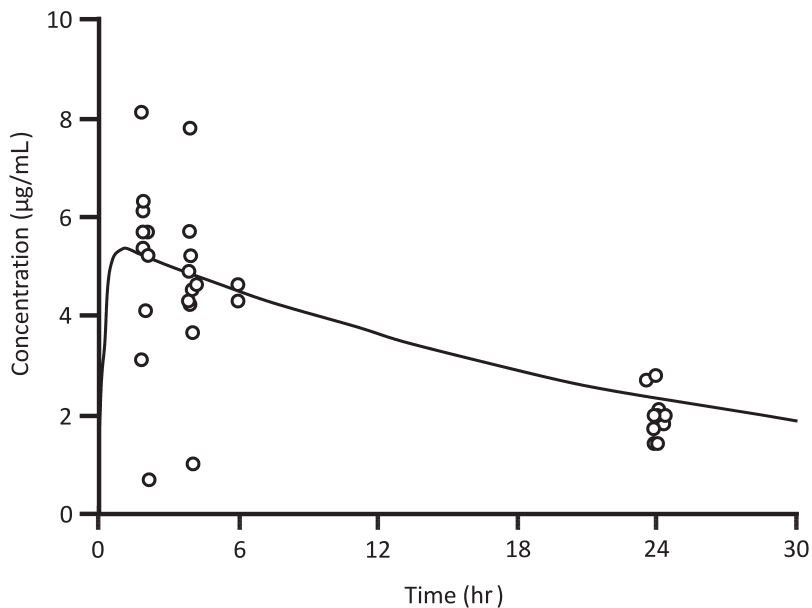


Table 2. Pharmacokinetic parameters of garenoxacin

	Mean \pm SD (%CV)				<i>p</i> value
	200 mg		400 mg		
CL (L/hr)	3.29 \pm 0.49	(15.0)	3.15 \pm 0.28	(8.97)	0.44
Vd (L)	66.1 \pm 15.1	(22.8)	62.5 \pm 10.9	(17.4)	0.55
K _a (hr ⁻¹)	2.12 \pm 0.14	(6.43)	2.14 \pm 0.06	(2.93)	0.61
K _e (hr ⁻¹)	0.0509 \pm 0.0082	(16.2)	0.0514 \pm 0.0079	(15.3)	0.89
AUC (μ g \cdot hr/mL)	62.3 \pm 11.9	(19.2)	128.0 \pm 12.5	(9.7)	<0.001
C _{max} (μ g/mL)	2.9 \pm 0.6	(20.7)	6.0 \pm 1.0	(17.2)	<0.001
T _{1/2} (hr)	13.9 \pm 2.2	(16.0)	13.7 \pm 1.9	(13.8)	0.84

CL: clearance, Vd: volume of distribution, K_a: first-order absorption rate constant, AUC: the area under the curve, C_{max}: peak concentration, K_e: elimination rate constant, T_{1/2}: half-life. The *t* test was used to analyze continuous variables.

tions derived from 20 patients. All patients were taken 2 to 4 samples in 24 hr after garenoxacin dose. Some predicted PK parameters are summarized in Table 2. There was no significant difference in parameters, except AUC and C_{max}, across the different dosage groups.

After single garenoxacin dosing, C_{max} at the 200 and 400 mg doses were proportionally increased and were within the range of 2.9 \pm 0.6 and 6.0 \pm 1.0 μ g/mL: *p* < 0.001, respectively. The corresponding values for AUC in plasma at the 200 and 400 mg doses showed similar tendency and were within the ranges of 62.3 \pm 11.9 and 128.0 \pm 12.5 μ g \cdot hr/mL: *p* < 0.001, respectively. The mean half-life (T_{1/2}) for garenoxacin appeared to be independent of dose (13.9 \pm 2.2 hr and 13.7 \pm 1.9 hr after 200 and 400 mg dose: *p* = 0.84) (Table 2).

Safety

There were no serious adverse events, suspected to be related with garenoxacin. Oral dose of garenoxacin (200 and 400 mg) were well tolerated.

Discussion

Garenoxacin is an oral fluoroquinolone with potent antibacterial activity against common respiratory pathogens, including resistant strains, such as multidrug-resistant *S. pneumoniae*, β -lactamase-producing *M. catarrhalis*, and BLNAR^{1~8}). As for quinolone antibacterial agents, the drug AUC/MIC ratio is the PD measurement that generally has the strongest correlation with outcome in non-clinical infection models and infected patients^{19, 20}). While the PD goal of therapy differs for Gram-positive and Gram-negative microorganisms, the probability for attainment of the target free AUC/MIC ratio estimated by Monte Carlo simulation was consistent with the actual efficacy of the phase III study for each strain in Japan^{11, 13}). And, previous studies have revealed that 400 mg once daily dose of garenoxacin for patients with normal to moderate renal

dysfunction has favorable PK profiles to show adequate antibacterial activity against common bacteria of respiratory infections^{10, 21, 22}).

Garenoxacin PK analysis have showed that WT, C_{cr} , gender and age were associated with statistically significant effects on its clearance and volume of distribution¹¹); approximately 20 to 50% of an administrated garenoxacin dose was excreted unchanged in the urine⁹). Additionally, *in vivo* animal studies have revealed that excretion of garenoxacin and its metabolites involves not only renal but also biliary pathways, while some studies have revealed that renal elimination is the major pathway^{9, 12}). Accordingly, there is a potential that PK of garenoxacin could be altered in subjects with severe renal impairment. However, no PK profile of garenoxacin in severe renal failure patients has evaluated.

In current PK analysis, when stratified by two dosages (200 and 400 mg), C_{max} and AUC were proportionally increased to garenoxacin dose (Table 1). Additionally, compared to Japanese healthy adult patients, both dose-level cohorts showed a decrease in mean C_{max} (200 mg; 2.9 versus 4.9 $\mu\text{g}/\text{mL}$, 400 mg; 6.0 versus 7.4 $\mu\text{g}/\text{mL}$), while mean AUC increased in both hemodialysis cohorts (200 mg; 62.3 versus 48.9 $\mu\text{g}\cdot\text{hr}/\text{mL}$, 400 mg; 128.0 versus 100.7 $\mu\text{g}\cdot\text{hr}/\text{mL}$)²³). Garenoxacin AUC and C_{max} were increased by 27% and lowered by 19%, respectively, in subjects with sever renal failure, compared with healthy volunteers. Mean CL of severe renal failure patients was lower than that of patients with normal renal function. Hence, severe renal failure patients demonstrated an increase in AUC compared to those with normal renal function. On the other hands, mean Vd of severe renal failure patients was bigger than that of patients with normal renal function. The increased Vd of garenoxacin, might derive from decreasing of protein binding and enhancement of permeability into some tissue, leaded a decreasing of C_{max} in severe renal failure patients. The $T_{1/2}$ for garenoxacin appeared to be independent of dose in our study (Table 2). And the $T_{1/2}$ was prolonged in subjects with sever renal impairment compared with healthy volunteers (13.7 versus 12.4 hr at 400 mg dose, respectively)²³). These data indicated that a possible requirement for dose modification with multiple dose.

Additionally, this study found that AUC after single oral garenoxacin dose (400 mg) for severe renal failure patients was approximately comparable with the AUC of healthy volunteers after administrated 600 mg once daily dose²³). GAJJAR, *et al.*⁹) also showed garenoxacin to be well tolerated when administered at doses up to 1200 mg for 14 days in healthy subjects. In subjects who were given 1200 mg, the mean AUC values for garenoxacin ranged from 205 to 471 $\mu\text{g}\cdot\text{hr}/\text{mL}$. In the multiple dose study of garenoxacin, with a single exception, all adverse events, such as headache, pharyngitis and dizziness, were mild or moderate in intensity and all were resolved without treatment; there did not appear to be any relationship between the garenoxacin dose and either the type or the frequency of adverse events, including abnormal clinical laboratory values. The average AUC observed in our study did not exceed values previously shown to be well tolerated⁹). Hence, changes in garenoxacin exposure for patients with severe renal failure do not ap-

pear to be clinically significant.

Moreover, fluoroquinolones have been reported that resistant mutants are selected exclusively within a concentration range (mutant selection window) between the mutant prevention concentration (MPC) and MIC^{24, 25)}. To restrict resistant mutants, the optimal dose needs to be selected in view of the maintenance of a trough concentration above the MPC of common bacteria, such as *S. pneumoniae*, *Staphylococcus aureus* and *H. influenzae*, is $<1 \mu\text{g/mL}$, the probability of having a trough concentration $>1 \mu\text{g/mL}$ was computed at several doses¹³⁾. In the mixed groups of healthy volunteers and moderate impair renal function, the probability for a trough garenoxacin concentration above the MPC ($1 \mu\text{g/mL}$) base on the plasma concentration of garenoxacin above the MPC is expected to exceed the MPC during the 400 mg treatment¹³⁾. Our data also revealed that garenoxacin concentrations at 24 hr after dose were higher than $1 \mu\text{g/mL}$ in subjects who were given 400 mg (Fig. 1). Accordingly, patients with severe renal failure are also expected to exceed the MPC with same dosage.

The limitations to our current study are that individual PK parameters were predicted based on the existed PK model based on the Phase I to III data conducted in Japan¹³⁾. However, the model had been subjected to a bootstrap analysis; the result of mean parameter estimates obtained from the bootstrap process (with 1,000 runs) were not statistically significantly different from the estimates previously obtained with the original data set. Another limitation is that garenoxacin was administrated as a single dose; thus, concentrations may not reflect those achieved with multiple dosing. However, previous study showed garenoxacin to be well tolerated when administered at doses up to 1200 mg for 14 days in healthy subjects⁹⁾, while a decreased CL in sever renal failure patients still suggested a possible requirement for dose modification with multiple dose. Finally, we did not evaluate the effects of hemodialysis on garenoxacin PK profile. However, previous study suggested that, in subjects receiving dialysis, removal of garenoxacin from systemic circulation was relatively insufficient (1.5% to 11.5%). And no need for a supplemental dose of garenoxacin after dialysis²⁶⁾, although it may be better to dose after hemodialysis for renal failure patients. Hence, over all these PK analysis support the 400 mg once daily garenoxacin regimen as effective treatment of respiratory tract infections, while the drug can exhibits modest an accumulation with multiple dosing that is consistent with its $T_{1/2}$.

In summary, this is the first study identified optimal garenoxacin dosing for severe renal failure patients receiving thrice-weekly hemodialysis. The PK of garenoxacin in the patients demonstrated a decrease in C_{max} and an increase in AUC compared to patients with normal renal function. While a prolonged $T_{1/2}$ in hemodialysis patients indicates a necessity for careful drug administration and suggests a possible requirement for dose modification when considering repetitive administration, 400 mg once-daily dose of garenoxacin, not 200 mg once-daily dose, was expected to be effective for severe renal failure patients infected with common bacteria of respiratory tract infections, as well as to prevent the emergence of resistant strain.

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Declaration of interest

This study is not funded any grants.

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