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□ ORIGINAL ARTICLE □

A Prospective Study of the Efficacy, Safety and Pharmacokinetics of Enteral Moxifloxacin in the Treatment of Hemodialysis Patients with Pneumonia

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Abstract

Objectives To investigate the efficacy of oral moxifloxacin (MFLX) as a treatment for pneumonia in hemodialysis (HD) patients and the pharmacokinetic (PK) profile of MFLX after oral administration.

Methods Thirteen adult patients who required HD due to chronic renal failure were enrolled in the present study, which was performed to investigate the treatment of community-acquired pneumonia in HD patients. A standard dose of MFLX (400 mg, once daily) was administered. The therapy was continued, discontinued, or switched to another antibiotic depending on the response of the pneumonia to MFLX. A population PK model was developed using the post-hoc method.

Results In total, 13 HD patients with pneumonia (male, n=7; female, n=6) were enrolled in the present study. The evaluation on the 3rd day showed that treatment was successful in 11 patients (84.6%) and that 10 patients were cured (76.9%). In the one case in which MFLX treatment failed, the patient was cured by switching to ceftriaxone (CTRX) (2 g, intravenously) plus levofloxacin (LVFX) (250 mg, orally). The causative bacterium in this male patient was *P. aeruginosa*. It did not display resistance to fluoroquinolones. One patient had liver dysfunction due to MFLX. The estimated PK parameters of MFLX were as follows: $AUC_{0\rightarrow24}$, 61.04±17.74 μg h/mL; C_{max}, 5.25±1.12 μg/mL; and C_{trough}, 1.15±0.45 μg/mL. The PK parameters of MFLX among the patients in whom adverse events occurred or in whom a cure was not achieved did not differ from those of the other patients to a statistically significant extent.

Conclusion MFLX showed good efficacy and safety in HD patients with community-acquired pneumonia and the results of the PK analysis were favorable. Further prospective studies with larger numbers of patients will be needed to draw definitive conclusions.

Key words: hemodialysis, pneumonia, moxifloxacin, pharmacokinetics

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Introduction

Moxifloxacin (MFLX) exhibits good antibacterial activity against Gram-negative and Gram-positive pathogens, including anaerobes and intracellular pathogens, and is a suitable agent for the empirical treatment of a variety of infections (1, 2). One of the major characteristics of MFLX is

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that the dosage does not need to be adjusted, even in patients with kidney disorders or those who are on hemodialysis (HD). Thus, it is prescribed as an ambulant treatment for mild pneumonia.

MFLX is specifically approved for treating infections of the respiratory tract [i.e. acute bacterial sinusitis, the acute exacerbation of chronic bronchitis and community-acquired pneumonia (CAP)] (3). Due to its spectrum of activity, it is also recommended for the treatment of hospital-acquired pneumonia (HAP) in selected patients (4). As with most fluoroquinolones, the oral bioavailability of MFLX is good (5, 6). This allows for intravenous administration to be switched to oral administration as soon as a patient's clinical conditions improve.

MFLX is reported to be effective for the treatment of pneumonia and it is not necessary to adjust the dose in HD patients; however, there have been no published studies on its clinical efficacy on pneumonia in HD patients or on the pharmacokinetics (PK) of MFLX in HD patients.

The Japanese Society for Dialysis Therapy reported that infectious diseases rank as the second cause of death in chronic HD patients and that the rate of death due to infectious disease in chronic HD patients has gradually risen since 1993-to the point that it is approaching the rate of death due to heart failure, which is the most common cause of death among these patients. Pneumonia in HD patients is especially concerning (7). One notable feature of MFLX, from the viewpoint of the drug metabolic route, is that it is eluted via the liver, not the kidneys-thus, it is not necessary to adjust the dose of the drug in patients with renal dysfunction or those who require HD (8).

MFLX can be expected to show high efficacy in the treatment of pneumonia in HD patients. However, to the best of our knowledge, the literature on the successful use of MFLX in the treatment of pneumonia does not include any studies involving HD patients. We therefore investigated the efficacy and safety of MFLX in the treatment of pneumonia in HD patients, with a particular focus on the PK parameters.

Materials and Methods

The study design and protocol

This prospective non-randomized study in HD patients was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee at the University of Oita (No. B10-048) and at each participating institution. Written informed consent was obtained from all of the patients or their legal representatives prior to their inclusion in the study. Adult HD patients with pneumonia who were treated as outpatients at four medical institutions specializing in dialysis in Oita Prefecture, Japan, were enrolled in the study and received MFLX treatment. The inclusion criteria were the appearance of a sudden pulmonary infiltrative shadow on a chest X- ray, an increased body temperature (>37.0℃), the characteristic clinical symptoms of pneumonia and an increased leukocyte count (>9,000/mm^3) or C-reactive protein (CRP) level.

The severity of pneumonia was evaluated according to the Pneumonia Patient Outcomes Research Team (PORT) score. The main exclusion criteria were abnormal liver function test results or cirrhosis, QT prolongation, hypokalemia, the use of a class IA or III anti-arrhythmic agent, pregnancy or possible pregnancy, an anamnestic history of convulsive disorder including epilepsy, previous fluoroquinolone treatment (for the present case of pneumonia), severe underlying disease, including cancer, heart failure and respiratory failure, no oral intake and PORT class V.

The administration of MFLX

MFLX was prescribed at the discretion of the attending physician alone and did not depend on potential study participation-the prescription of additional or alternative agents and the discontinuation of MFLX due to microbiological results or changes in the clinical conditions was decided in the same manner. The participants took MFLX (400 mg, orally, once daily) in compliance with the basic recommended dose in Japan. The treatment period was in accordance with the Nursing and Healthcare-associated Pneumonia (NHCAP) guidelines provided by the Japanese Respiratory Society (JRS) (9). The therapy was continued or discontinued or switched to other antibiotics depending on the response of the pneumonia to MFLX, including the achievement of a cure, the lack of apparent improvement or adverse effects. Safety assessments included the documentation of adverse events, the continuous monitoring of vital signs, a physical examination and daily clinical laboratory testing, which were performed as part of the patients' routine care. At a minimum, electrocardiograms were assessed before the first dose and after the last dose.

Evaluation methods

The treatment was evaluated according to the guidelines of the Japanese Society of Chemotherapy (JSC) (10). Briefly, clinical efficacy was evaluated at three days after the start of MFLX treatment, at the end of therapy (EOT) and the test of cure (TOC), which was the primary endpoint, was evaluated at 5-7 days after the initiation of treatment. Adverse events were defined as adverse reactions with an undeniable causal relationship with the administration of MFLX.

Analytical methods

At least 2 points of post-MFLX treatments (trough) were evaluated. Laboratory blood tests were performed twice at 3 days after the initiation of MFLX treatment. All plasma specimens were stored at -20℃ until the analysis. The MFLX concentration in plasma was determined by reversed phase high performance liquid chromatographic (HPLC) and fluorometric detection (11). The lower limit of quantification was 0.020 mg/L. The intra-assay and inter-assay imprecision

Table 1. Clinical Characteristics of the Patients and Causative Bacteria.

Case	Age (year)	Sex	Body dry weight (kg)	Periods of HD (months)	Inpatient/ Outpatient	PORT Class	Underlying diseases excluding kidney disorder	Administration days of MFLX (days)	Causative bacteria
1	70	M	51.0	160	I	IV	DM,	7	*Haemophilus influenzae*
2	68	M	51.0	131	O	IV	HT, CD	6	*Haemophilus influenzae*
3	68	F	44.5	4	O	IV	DM, HT, BA	8	*Moraxella catarrhalis*
4	70	F	58.0	13	O	III	PCK	7	*Pseudomonas aeruginosa*
5	47	F	77.0	47	O	II	DM, HT	5	
6	56	F	51.7	200	I	IV	HT	8	*Pseudomonas aeruginosa*
7	78	F	47.0	36	I	IV	HT	9	
8	72	M	52.0	62	O	IV	DM	5	
9	76	M	53.5	132	O	IV	DM, HT, CD	3	
10	70	M	64.5	64	O	IV	CD	7	
11	71	M	46.0	43	O	IV	HT,CD	12	*Staphylococcus aureus*
12	52	F	81.0	161	O	III	HT	8	
13	70	M	51.2	150	O	IV	DM, HT, CD	5	

M: male, F: female, I: inpatient, O: outpatient, PORT: Pneumonia Patient Outcomes Research Team, DM: diabetes mellitus, HT: hypertension, CD: cardiac disease, BA: bronchial asthma, PCK: polycystic kidney, MFLX: moxifloxacin

and bias, which were calculated from co-analyzed quality control samples in spiked plasma, were <5%.

The population PK analysis and evaluation

We outsourced the data analysis to Bell Medical Solutions, Tokyo, Japan. Briefly, the area under the curve during one dose ($AUC_{0\rightarrow24}$), the maximum concentration observed at a steady state ($C_{max\ ss}$) and the trough concentration at a steady state ($C_{trough\ ss}$) were evaluated in participants who took MFLX (400 mg, orally).

Results

Patients' backgrounds

Thirteen HD patients with pneumonia (male, n=7; female, n=6) were enrolled in the present study. The detailed patient data are shown in Table 1. In summary, the median age was 66.8 years (range, 47-78 years), the median body weight was 56.0 kg (range, 44.5- 81.0 kg) and the median HD period was 92.5 months (range, 4-200 months). Ten of the participants were outpatients, and 3 were inpatients. The patients' PORT scores were classified as class II (n=1) class III (n=2) class IV (n=10). Their complications included kidney disorder (n=13 [all]), hypertension (n=9), diabetes mellitus (n=6) and cardiac disorder (n=5). All patients received MFLX for the treatment of suspected pneumonia. The treatment period was 6.9±2.3 days.

The clinical efficacy of MFLX

The clinical efficacy of MFLX for the treatment of pneumonia in HD patients was measured according to the JSC guidelines. Early efficacy, at 3 days after the start of MFLX, was observed in 84.6% (11/13) of the patients; 84.6% (11/13) at the EOT of MFLX and 76.9% (10/13) at the TOC of MFLX. At the EOT, an X-ray examination revealed no improvement of the infiltration shadow in one case (Case 4) at the EOT (7 days); furthermore, the patient's CRP had increased (from 2.58 to 11.05 mg/dL). Case 4 was finally cured by switching to ceftriaxone (2 g, intravenously) plus levofloxacin (LVFX, 250 mg, orally). The causative bacterium in Case 4 was *P. aeruginosa*, which showed no resistance to LVFX (the susceptibility to MFLX was not tested). Another case (Case 8) was judged to be "indeterminable" at the EOT due to liver dysfunction on day 5 after the initiation of MXFL treatment. Case 7 was diagnosed as "not cured" by the TOC; the patient had a fever but no progressive pneumonia on a chest X-ray taken a week after the termination of MFLX treatment without the definitive identification of a causative microorganism. Thus, additional MFLX treatment was initiated based on the physician's decision. The cause of this fever was undetermined.

Causative bacteria

Causative bacteria were isolated from the cultures of sputum samples from 6 patients (Table 1). *H. influenzae* and *P. aeruginosa* were representatively isolated (n=2, each). All patients had mono-microbial infection (not mixed infection). Moreover, a bacterial evaluation showed that the causative bacteria disappeared or was predicted to have disappeared after the administration of MFLX.

Adverse events

One patient had liver dysfunction on day 5 after the initiation of MXFL. He had a good early response to MXFL but the treatment was discontinued from the 6th day without a recurrence of pneumonia or additional antibiotic treatment.

PK in MXFL

The data of 7 of the patients (Cases 7-13) were sufficient for a PK evaluation (Table 2). In summary, the estimated PK parameters of MXFL were as follows: $AUC_{0\rightarrow24}$, 61.04±17.74 μg h/mL; C_{max}, 5.25±1.12 μg/mL; and C_{trough}, 1.15±0.45 μg/mL. The PK parameter values of the cases with adverse

Table 2. Pharmacokinetics Parameters and Clinical Efficacy.

Case	Age	MFLX dosing	$AUC_{0\text{-}24\ ss}$	$C_{max\ ss}$	$C_{trough\ ss}$	Efficacy		
		(days)	(μg·h/mL)	(μg/mL)	(μg/mL)	EOT	TOC	Adverse events
7	78	9	92.12	7.21	1.85	effective	not cured	
8	72	5	53.00	5.03	0.91	effective	cured	Liver dysfunction
9	76	3	63.17	5.41	1.24	effective	cured	
10	70	7	42.24	4.01	0.69	effective	cured	
11	71	12	70.08	5.82	1.44	effective	cured	
12	52	8	41.08	3.93	0.57	effective	cured	
13	70	5	65.56	5.35	1.35	effective	cured	
Average			61.04±17.74	5.25±1.12	1.15±0.45			

AUC: area under the blood concentration-time curve, EOT: end of therapy, TOC: test of cure

events such as liver dysfunction (Case 8) and the case that was "not cured" (Case 7) by MXFL showed no significant differences when they were compared to the other cases or the subgroup of cases in which a PK evaluation could be performed.

Discussion

MFLX is approved as an oral antimicrobial agent and is thus widely used for the treatment of pneumonia. No dosage adjustment is required in elderly individuals or in HD patients. However, the precise PK/PD data for plasma MFLX among HD patients suffering from mild pneumonia is important information and the current data are quite limited. In the present study, we first evaluated MFLX (400 mg, orally, once daily) in HD patients with mild pneumonia.

There are few reports on the causative bacteria of pneumonia in HD patients. A report from Spain regarding the causative bacteria of community-acquired pneumonia in 203 chronic kidney disease patients, including 44 HD patients, showed that *Streptococcus pneumoniae* was most frequently isolated (28.1%), followed by *Haemophilus influenzae* and atypical bacteria (7). These characteristics showed no remarkable differences from usual CAP (9). This was similar to the finding of our study. A large scale study (n=10,365) on HD-associated pneumonia in the United States showed that *Streptococcus pneumoniae* was the bacterium that was most frequently isolated, followed by *P. aeruginosa* and *Klebsiella pneumoniae,* and that *S. aureus* was very rare in patients who were hospitalized for pneumonia (12).

A Japanese HD-associated pneumonia study (n=71) demonstrated the causative bacteria in 48 patients, and found that *S. aureus* was the most common bacterium (n=14, 29.1%) followed by *Enterococcus*, *Klebsiella pneumoniae,* and *P. aeruginosa* (13). Another study of HD-associated pneumonia (n=69) in 2011 reported that *S. aureus* was the most common bacterium (26 cases, 37.7%) followed by *Streptococcus pneumoniae, Klebsiella pneumoniae* and *Haemophilus influenzae* (14). Similarly, in our study *H. influenza* and *P. aeruginosa* were isolated, but not *Streptococcus pneumoniae.* The guidelines for pneumonia from American Theoretic Society and the Infectious Disease Society of America included HD-associated pneumonia in the category of health care-associated pneumonia (4), while the NHCAP guidelines from the JRS, which were established in 2011, included HD-associated pneumonia in the category of NHCAP (9). Because of the high risk of antibiotic resistance, which is similar to HAP, attention needs to be paid to the difference from CAP with regard to antibiotic selection. The question of how HD-associated pneumonia is categorized should be resolved by the medical and nursing care system. It is presumed that differences will exist in dialysis patients, among patients with different performance statuses, and among different countries, regions and medical facilities.

One of the major characteristics of MFLX is that the dosage does not need to be adjusted, even for HD patients. Dosage adjustments involve important changes in the volume of distribution and/or the clearance of the drug, which affects drug exposure and which may lead to therapeutic failure or an adverse drug reaction (7, 8). This study showed the efficacy of MFLX in the treatment of HD-associated pneumonia, while the results of the PK analysis were favorable. These aspects have not been fully understood or studied in HD patients. From the viewpoint of antibiotic metabolism in HD patients in comparison to healthy volunteers, the median PK parameters of $AUC_{0\rightarrow24}$, C_{max} and C_{trough} did not differ to a statistically significant extent, which is in agreement with previous reports (15). Thus, it was found that the clearance of MFLX was not affected by stable chronic renal disease. It is argued that alternative routes of elimination (i.e. excretion of the unchanged or conjugated drug in the feces) fully compensates for the reduced renal excretion of MFLX in these patients.

Our data showed no significant differences in the PK parameters of the successfully-treated group and the treatment failure group. This result suggests that the PK parameters were not involved in the treatment success or failure in HD-associated pneumonia. Other factors, such as the causative pathogen or the condition of the patients might have been related to the treatment outcome (16).

Previous reports involving the analysis of PK parameters associated with MFLX treatment mostly included patients who had continuous hemodiafiltration or peritoneal dialysis;

as mentioned above, the data from HD patients were limited (17, 18). Our data showed no significant differences in comparison to the results of 9 non-HD patients with bacterial pneumonia who received MFLX in a Japanese clinical trial (19). The parameters in that trial were as follows: $AUC_{0\rightarrow24}$, 38.9-65.42 μg h/mL; C_{max}, 3.69-5.47 μg/mL; and C_{trough}, 0.57-1.21 μg/mL.

Our data showed that there was no significant relationship between the concentration of MFLX in HD patients and the effect on pneumonia; however, the number of patients, especially those for whom data on the MFLX PK/PD were available, was limited. A detailed analysis of the clinical efficacy would require a larger number of patients. The patient in the one case in which MFLX treatment failure occurred-who was diagnosed as "not cured" at the TOC-had higher than average $AUC_{0\rightarrow24\ ss}$, $C_{max\ ss}$ and $C_{trough\ ss}$ values (Case 7). This patient had fever at one week after the termination of MFLX treatment; subsequently, additional MFLX was given and the fever diminished. There was no definitive identification of causative microorganism and it is possible that the patient's fever was caused by a different infection.

In conclusion, this study demonstrated that MFLX can be safely and effectively used in the treatment of HD patients with pneumonia, with a low incidence of adverse events and that the PK parameters in such patients are appropriate. Further studies, involving a greater number of patients, would allow for more detailed comparisons with other treatments.

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The authors state that they have no Conflict of Interest (COI).

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