Abstract

Continuous renal replacement therapy (CRRT) is a common technique in critically ill patients. However, there is no uniformity in the pharmacokinetics of ciprofloxacin (CPFX) used during CRRT. The aims of present study were to estimate the pharmacokinetics of CPFX and to determine the appropriate administration of CPFX for critically ill patients undergoing CRRT. CPFX total clearance (CL_{tot}) was calculated based on the creatinine clearance (CL_{cre}), dialysate flow (Q_D) and ultrafiltrate flow (Q_F) as follow: $CL_{tot\ (l/h)} = (4.83\ CL_{cre\ (l/h)} + 6.41) + 0.92\ (Q_D+Q_{F\ (l/h)})$ base on *in vitro* study using CRRT circuit model. We administered CPFX to critically ill patients based on the CL_{tot}, which was 50 x $CL_{tot\ (l/h)}$ (mg/day). We confirmed that the CPFX concentrations reached higher than optimal concentrations and the infections were all successfully controlled in these patients.

Continuous renal replacement therapy (CRRT) is a common technique to treat renal failure in critically ill patients. However, there is no uniformity in the pharmacokinetics of the drugs used during CRRT. Ciprofloxacin (CPFX) is used in the treatment for severe infections [1]. However, the pharmacokinetics of CPFX are affected by both the renal function and CRRT [2,3]. The aim of present study was to establish a wide use dosage-regimen method to calculate the optimal dosage for CPFX in critically ill patients during CRRT. For this purpose, we examined as follows: 1) estimated the CPFX total clearance (CL_{tot}) during CRRT based on dialysate flows (Q_D), the ultrafiltrate flows (Q_F), and renal function of the patient, 2) determined the appropriate dose of CPFX based on the CL_{tot}, and 3) confirmed CPFX pharmacokinetics in critically ill patients receiving CRRT when the dose determined based on CL_{tot} was administered.

Materials and Methods

1) To estimate CL_{tot} during CRRT

A CRRT system (ACH-10, Asahi Medical Co., Japan) was used. A CRRT circuit was set up using a cellulose triacetate hollow fiber 1.1 m^2 hemofilter (UT-110, Nipro, Japan). The machine was primed with a 5% bovine serum albumin (BSA) solution. Twenty mg of CPFX were added to 200 ml of the 5% BSA solution in the reservoir. The CRRT conditions were as follows: the BSA solution flow was fixed at 9 l/h; Q_D was defined from 0, 1, and 2 l/h; Q_F was defined from 0, 1, and 2 l/h independently of Q_D; normal saline was used as a

dialysate and it also served as a replacement fluid which was infused post-dilusionally with an equal amount of Q_F. We took samples from the pre-hemofilter and the filtrates at 15, 30, 45, and 60 min after the start of CRRT. Each variation was performed twice and the clearance by CRRT (CL_{CRRT}) was calculated 2 times based on Q_D, Q_F, and CPFX concentrations in the filtrate and pre-hemofilter. The concentrations of CPFX were determined using the high-performance liquid chromatography method [4].

CPFX clearance in patients (CL_{vivo}) was based on the creatinine clearance (CL_{cre}) in previous study [2]. The CPFX CL_{tot} in a patient during CRRT was calculated as follows:

$$\begin{aligned} \text{CPFX } CL_{tot\ (l/h)} &= CL_{vivo} + CL_{CRRT} \\ &= (4.83\ CL_{cre\ (l/h)} + 6.41) + CL_{CRRT\ (l/h)} \end{aligned} \quad (1)$$

2) To determine the appropriate dose of CPFX

Clinical success has been obtained when the target of the area under the plasma concentration-time curve (AUC) $_{[(mg/l)\cdot h]}$ / minimum inhibitory concentration (MIC) $_{(mg/l)} \geq 100\ _{(h)}$ [5]. In a majority of bacteria, the MIC required to inhibit the growth of 90% of the strains for CPFX was <0.5 mg/l [1]. Therefore, we determined the target of AUC to be ≥50 [(mg/l)·h]. We determined the optimal dose to be 50 x $CL_{tot\ (l/h)}$ (mg/day) in order to maintain the target of AUC based on the CL_{tot}.

3) To confirm CPFX pharmacokinetics in critically ill patients receiving CRRT

Three patients with acute renal failure were studied. **Table 1** shows the patients' clinical backgrounds. In all patients, CL_{tot} was calculated and the optimal CPFX doses determined based on the CL_{tot} were administered intravenously. A CRRT system (JUN600, UBE, Japan) was used. The same hemofilter as that used in the *in vitro* study was used. The dialysate and replacement fluid were Sublood-A® (Fuso, Japan). The CRRT conditions were as follows: The blood circuit pumped 6 l/h; Q_F was defined as 1.0 l/h in all patients; Q_D was infused in a countercurrent at rates of 1.0 l/h. The replacement fluid was infused after dilution as clinically indicated. The sampling points were pre-hemofilter and the filtrates. The samples were taken before the start of the next CPFX administration, at 1, 1.5, 2, 6, and 12 h after the start of the drug administration. The CPFX concentrations were determined by the high-performance liquid chromatography method [4]. A pharmacokinetic analysis was performed using the nonlinear least-squares regression program [6]. The parameters were calculated by a two-compartment open model with a constant rate of infusion. The AUC was calculated using the trapezoidal rule.

Results

CL_{CRRT} obtained by interpolation into a simple linear regression of CL_{CRRT} against Q_D+Q_F closely correlates with the experimental data (**Figure 1**). CPFX CL_{tot} was calculated as follows:

$$CL_{tot\ (l/h)} = (4.83\ CL_{cre\ (l/h)} + 6.41) + 0.92\ (Q_D + Q_{F\ (l/h)}) \quad (2)$$

CL_{tot} in the patients were presented in **Table 1**. The CPFX doses in all patients were set 600 mg/day. CPFX at a dose of 300 mg was administered during a 60 min period every 12 h. The CPFX concentrations curve was presented in **Figure 2**. **Table 2** shows the pharmacokinetic parameters. The mean of actual AUC reached a level higher than the target AUC. The infections of the patients were successfully controlled.

Discussion

Several reports have described the achievement of AUC/MIC ≥100 to demonstrate a good clinical outcome [5]. However, a high dose of CPFX is needed to achieve the target of AUC/MIC. Lipman *et al.* [7] concluded that an intravenous dosage of 400 mg 3 times daily was safe and effective in patients with severe sepsis. In a clinical study, we confirmed that the actual AUC [54.9±12.8 (mg/l)·h] was higher than the targeted AUC [50 (mg/l)·h], when the CPFX amounts, based on the CL_{tot}, were intravenously administered. This result showed that the CL_{tot} formula as determined based on the findings of an *in vitro* study is therefore appropriate.

In CRRT, high-flux membranes with large pores and no drug-adsorption are recommended. The hemofilter used in this study was a cellulose tri-acetate membrane with the recommended characteristics. The pore size of the

hemofilter may not influence the CL_{CRRT} because of the sufficiently low molecular weight of CPFX [1,4]. The surface area of the hemofilter may affect the clearance of small solute when Q_D is large amount [8]. Therefore, the results of the present study are not considered to be adaptable to the follow situations: 1) the hemofilter has drug-adsorption ability; 2) when Q_D is a large amount, then the hemofilter has a much different surface area from that used in the present study.

In conclusion, we estimated CL_{tot} during CRRT based on Q_D, Q_F, and renal function of the patient. We established a wide use dosage-regimen calculation of CPFX, which was 50 x [(4.83 CL_{cre} + 6.41) + 0.92 (Q_D+Q_F)] (mg/day) in critically ill patients during CRRT. Furthermore, we confirmed that the wide use dosage-regimen method is also appropriate in a clinical setting.

References

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Figure Legends

Figure 1. CPFX clearance by CRRT based on an *in vitro* study. A simple linear regression analysis revealed a strong correlation between CL_{CRRT} and $Q_D + Q_F$. Circles indicate CPFX CL_{CRRT} in each variation of CRRT settings. The line is the regression line.

Figure 2. The plasma CPFX concentration-time curve at a CPFX administration of 300 mg every 12 h. The circle and bar indicate the mean and standard deviation of CPFX concentration.

Table 1. Characteristics of the Patients

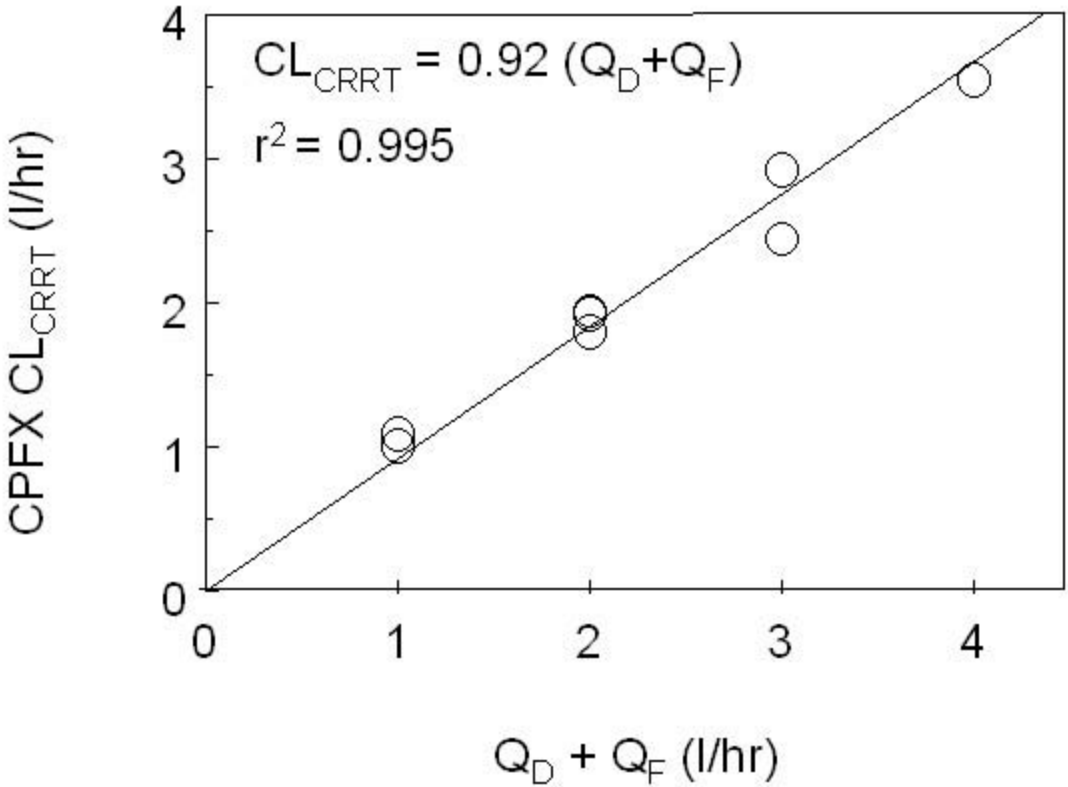
Patient	Gender	Age (years)	Weight (kg)	APACHE-II	Urea nitrogen (mmol/l)	24-hour CL_{cre} (l/h)	Predictive CL_{CRRT} (l/h)	Predictive CL_{tot} (l/h)
1	male	75	59	36	38	1.68	1.84	16.4
2	male	77	64	42	19	0.86	1.84	12.4
3	male	41	65	19	29	0	1.84	8.3
Mean ± SD		64 ± 20	62 ± 3	32 ± 12	29 ± 10	0.85 ± 0.84	1.84	12.4 ± 4.1

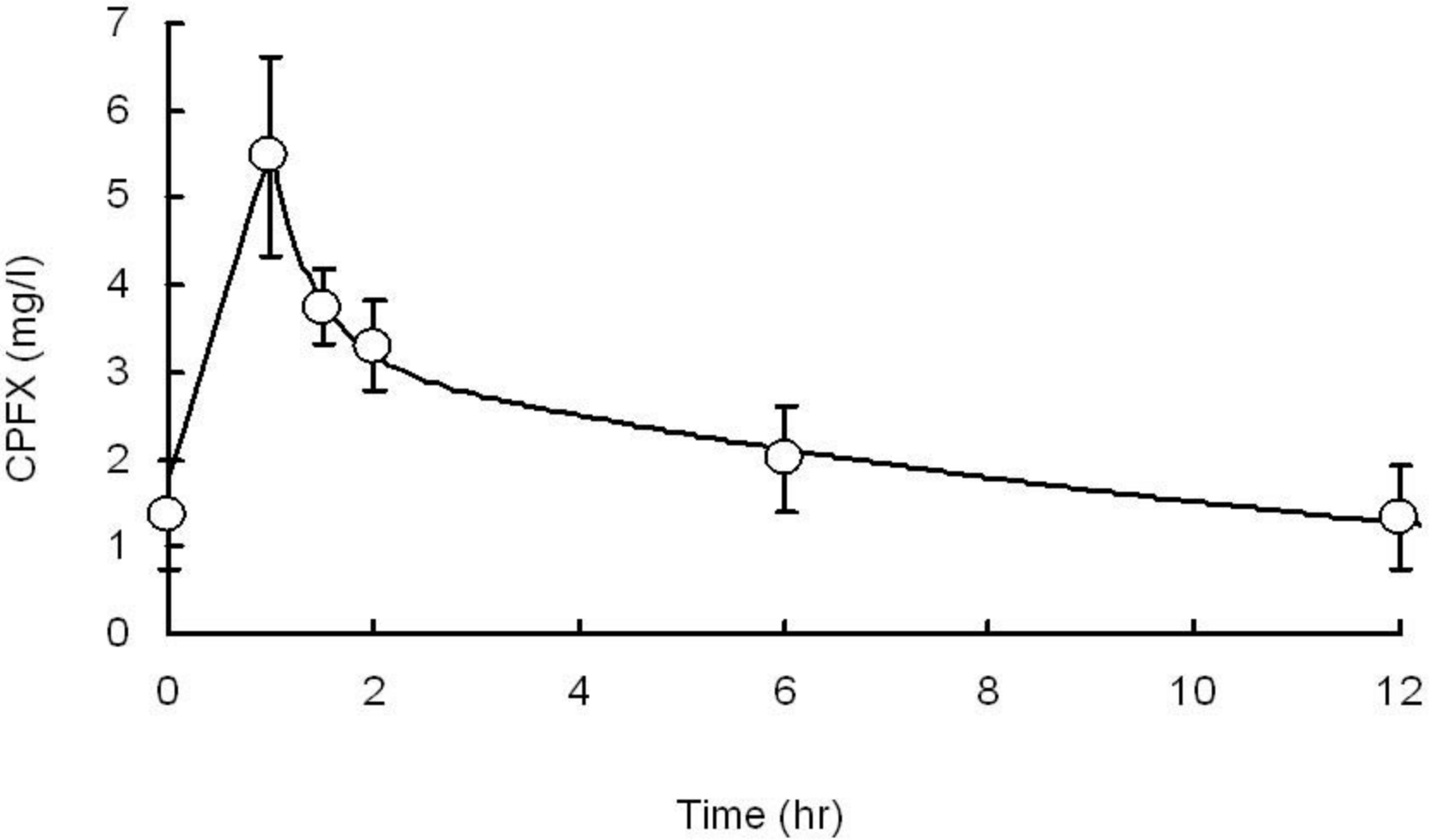
APACHE-II, Acute Physiology and Chronic Health Evaluation II score; CL_{cre}, Creatinine clearance;CL_{CRRT};clearance by continuous renal replacement therapy; CL_{tot},total clearance.

Table 2. Pharmacokinetic Parameters of Ciprofloxacin in the patients during Continuous Renal Replacement Therapy

Patient	CL_{CRRT} (l/h)	CL_{tot} (l/h)	$t_{1/2}$ (h)	V_{ss} (l)	AUC [(mg/l)·h]
1	1.78	14.6	4.93	99.1	42.1
2	1.81	6.3	9.74	85.7	54.8
3	1.75	5.4	10.9	82.7	67.8
Mean ± SD	1.77 ± 0.03	8.8 ± 5.1	8.52 ± 3.16	89.2 ± 8.7	54.9 ± 12.8

$CL_{CRRT,}$ clearance by continuous renal replacement therapy; CL_{tot}, total clearance; $t_{1/2}$, a half–life; V_{ss}, steady state volume; AUC, Area under the concentration–time curve.


$CL_{CRRT} = 0.92 (Q_D+Q_F)$
$r^2 = 0.995$
CPFX CL_{CRRT} (l/hr)
$Q_D + Q_F$ (l/hr)
0
1
2
3
4


7
6
5
4
3
2
1
0
CPFX (mg/l)
0
2
4
6
8
10
12
Time (hr)