An evaluation of ciprofloxacin pharmacokinetics in critically ill patients undergoing continuous veno-venous haemodiafiltration

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Abstract

Background: The study aimed to investigate the pharmacokinetics of intravenous ciprofloxacin and the adequacy of 400 mg every 12 hours in critically ill Intensive Care Unit (ICU) patients on continuous veno-venous haemodiafiltration (CVVHDF) with particular reference to the effect of achieved flow rates on drug clearance.

Methods: This was an open prospective study conducted in the intensive care unit and research unit of a university teaching hospital. The study population was seven critically ill patients with sepsis requiring CVVHDF. Blood and ultrafiltrate samples were collected and assayed for ciprofloxacin by High Performance Liquid Chromatography (HPLC) to calculate the model independent pharmacokinetic parameters; total body clearance (TBC), half-life (t½) and volume of distribution (Vd). CVVHDF was performed at prescribed dialysate rates of 1 or 2 L/hr and ultrafiltration rate of 2 L/hr. The blood flow rate was 200 ml/min, achieved using a Gambro blood pump and Hospal AN69HF haemofilter.

Results: Seventeen profiles were obtained. CVVHDF resulted in a median ciprofloxacin t½ of 13.8 (range 5.15-39.4) hr, median TBC of 9.90 (range 3.10-13.2) L/hr, a median Vdss of 125 (range 79.5-554) L, a CVVHDF clearance of 2.47 +/-0.29 L/hr and a clearance of creatinine (Clcr) of 2.66 +/-0.25 L/hr. Thus CVVHDF, at an average flow rate of ~3.5 L/hr, was responsible for removing 26% of ciprofloxacin cleared. At the dose rate of 400 mg every 12 hr, the median estimated Cmax/MIC and AUC0-24/MIC ratios were 10.3 and 161 respectively (for a MIC of 0.5 mg/L) and exceed the proposed criteria of >10 for Cmax/MIC and > 100 for AUC0-24/MIC. There was a suggestion towards increased ciprofloxacin clearance by CVVHDF with increasing effluent flow rate.

Conclusions: Given the growing microbial resistance to ciprofloxacin our results suggest that a dose rate of 400 mg every 12 hr, may be necessary to achieve the desired pharmacokinetic - pharmacodynamic (PK-PD) goals in patients on CVVHDF, however an extended interval may be required if there is concomitant hepatic impairment. A correlation between ciprofloxacin clearance due to CVVHDF and creatinine clearance by the filter was observed (r² = 0.76), providing a useful clinical surrogate marker for ciprofloxacin clearance within the range studied.

Trial Registration: Current Controlled Trials ISRCTN52722850

Background

Severe sepsis is a significant contributor to Intensive Care Unit (ICU) admission and reports vary from 12% to 27% of ICU admissions in different countries [1]. Many more patients develop sepsis following ICU admission. EPIC 2 demonstrated that 51% of ICU inpatients were classified as infected on the day of the point prevalence study. In this study 62% of isolates were identified to be Gram negative, which is worrisome given the dearth of in-development antimicrobials with gram negative coverage [2]. Under dosing of antibiotics has enabled the genesis of resistant strains and this is particularly an issue with fluoroquinolones, aminoglycosides and beta lactams [3,4]. Of particular concern is the ability of fluoroquinolones to engender resistance to other classes of antibiotics [5]. Altered drug
Cpmax is the maximum steady state serum concentration, practice, Cpmax is equated with the serum peak level. A as predictors of therapeutic efficacy [10-12]. In clinical continuous veno-venous haemofiltration (CVVH) [20].

increased drug clearance via CVVHDF compared to determinant of the effect of CRRT on clearance, with the time during continuous renal replacement therapy (CRRT), the method of CRRT used has been presented as an important determinant of the effect of CRRT on clearance, with increased drug clearance via CVVHDF compared to continuous veno-venous haemofiltration (CVVH) [20]. Nonetheless, clearance via CVVH of up to 25% has been reported [21]. It has been recommended therefore that dosing during CVVHDF is focussed on attaining clinically adequate drug concentrations, preferably with concurrent therapeutic drug monitoring.

As a result of the reported variability in ciprofloxacin pharmacokinetic parameters during critical illness, differences in patient populations and CRRT conditions in literature reports and the absence of a consensus on dosing regimens, a prospective pharmacokinetic evaluation of ciprofloxacin during CVVHDF therapy was undertaken.

Methods- Patient Demographics and Clinical Characteristics
This was an open, prospective pharmacokinetic study in a multidisciplinary, intensive care unit in a university teaching hospital. Ethics approval was obtained from the Joint Ethics Committee (St James's/AMNCH) (Reference Number 041008/7804). Clinical trial approval was granted by the Irish Medicines Boards (EudraCT Number 2004-002195-42) and the trial was registered with Current Clinical Trials (ISRCTN52722850). Consent (predominantly consent by proxy) was obtained in compliance with Helsinki declaration. Seven critically ill patients, treated concurrently with intravenous ciprofloxacin and CVVHDF therapy, were enrolled in the study. Intravenous ciprofloxacin 400 mg twice daily administered as a one hour infusion was the dosage regimen generally employed, dosing at all times was at the discretion of the physician. A dosage regimen of ciprofloxacin 400 mg once daily was also analysed for three patients, while a dosage regimen of 200 mg twice daily was also assessed in one patient. MIC susceptibility testing for pathogens isolated was not performed. Instead a representative MIC of 0.5 mg/L was employed based on an analysis of local ecology data. It should be noted that CVVHDF patients in this hospital are prescribed on average 14.3 drugs during CVVHDF, 4.7 +/-2.66 are anti-infectives.

CVVHDF conditions
CVVHDF was performed at prescribed dialysate rates of 1 or 2 L/hr and ultrafiltration rate of 2 L/hr. This reflects the typical CVVHDF prescription of the unit. The blood flow rate was 200 ml/min, achieved using a Gambro blood pump and Hospal AN69HF haemofilter. For patients 6 and 7, CVVHDF was run heparin-free, due to coagulopathy.

Measurement of Ciprofloxacin Concentrations
Timed serum samples were collected during each dosage interval and ultrafiltrate during 7 dosage intervals (1 per patient). Effluent fluid was collected for the entire dosage interval. The volume of each hourly batch was recorded and a 40 ml sample was taken for analysis. Aliquots from each sample were analysed for...
ciprofloxacin concentration and for creatinine determination. Total ciprofloxacin concentrations in serum and effluent were measured by the HPLC method of Davis et al [22], adapted for both serum and effluent fluid analysis. Quantitation was based on external standard calibration using the ratio of the peak areas of the analyte and the internal standard (β-hydroxypropyl theophylline). Replicate analysis was performed both on control samples and study samples. Ciprofloxacin hydrochloride monohydrate (1g) (gift from Bayer UK) was used to verify the concentration of the commercial infusion solution, Ciproxin®. The extraction efficiency was in excess of 80% in the concentration range 0.5-20.0 μg/ml and the between day coefficient of variation <10%. Precision was less than 5.0 R.S.D.%. The sensitivity of the assay was 0.5 μg/ml.

**Analysis of Serum Concentrations of Ciprofloxacin**

Serum concentrations, from an indwelling arterial cannula, were measured immediately before the infusion was started, immediately after the infusion finished and at 2,3,4,6,8 and 12 hours post infusion where the dosage interval was 12 hr. When the prescribed dosage interval was 24 hr samples were also taken at 18 and 24 hrs. Exact sampling times were recorded. Thus Cmax was directly measured.

**Pharmacokinetic analysis**

**Calculating half-life and clearance**

Non-compartmental pharmacokinetic methods were used. Pharmacokinetic analysis was performed using WinNonlin pharmacokinetic software, version 5.2, (Pharsight Corporation, North Carolina, U.S.A.). The terminal half-life (t1/2) was calculated as 0.693/λz, where λz is the first order terminal elimination rate constant. The area under the plasma concentration-time curves (AUC) were calculated using the linear trapezoidal method. AUC for the study period (n = 12 or 24 hours) was used to calculate the AUC extrapolated to infinity (AUC0–∞) by the equation AUC0–τ + C* / λz where C* is the final plasma concentration, at the final sampling time, τ. The Total Body Clearance (TBC) was calculated as dose/AUC0–∞ for profile 4a as this was a first dose, and as dose/AUC0–τ at steady state, where τ is the dosage interval, for all other profiles except 2c, 4b and 6c, which were not at steady state.

**Estimating clearance for profiles not at steady state**

Profiles 2c, 4b and 6c did not result from initial doses, and could not be considered to be at steady state as they directly followed a change in dose or interval. For these profiles, TBC was estimated as dose/AUC0–∞.

AUCn0–∞ in these cases was estimated as (AUCn0–∞−(C*(n–1)/λz(n–1))), where C*(n–1) was the final observed concentration at the end of the preceding dose interval, and λz(n–1) was the first order terminal elimination rate constant calculated from the preceding dose interval.

**Calculating volume of distribution at steady state (Vdss)**

Because of the severity of illness body weights could not be accurately monitored, consequently parameters were not weight normalised. Volume of distribution at steady state (Vdss) for an initial dose was calculated as TBC × (((AUMC0–∞/AUC0–∞) − τinf/2)), where τinf is the duration of the infusion, and as TBC × (((AUMC0–τ + τ(AUC0–∞ − AUC0–τ))/AUC0–τ) − τinf/2) from profiles at steady state. In cases where the dosing interval was changed from 24 (at steady state) to 12 hours, the first profile following the change was calculated as a 24 hour interval, with sampling ceasing at 12 hours. This was the case for profiles 6b and 7b. Vdss was not calculated for profiles 2c, 4b and 6c as these were neither an initial dose or at steady state.

**Calculating sieving coefficients**

Sieving coefficients (S) for ciprofloxacin and creatinine were calculated from the time-matched concentrations in effluent and in serum for a single dosage interval, whereby Screat = Ceffluent/Cserum and Scipro = Ceffluent/Cserum. The clearance of creatinine was calculated from Screat and the measured flow of effluent (Q) where Clcreat = Screat × Q.

The fraction cleared by CVVHDF (FCVVHDF) was determined from CLCVVHDF/TBC. The PK-PD parameters Cpmax/MIC and AUC0–24/MIC were employed as predictors of the likelihood of clinical and microbiological response.

**Results**

**Patients**

Relevant demographic and clinical data relating to the seven patients studied are presented in Table 1. Patients were severely ill having renal failure, haemodynamic instability and coagulopathy. Six patients were prescribed ciprofloxacin for documented infection (Pseudomonas aeruginosa, Escherichia coli), while one patient with suspected sepsis was prescribed ciprofloxacin empirically. The median APACHE II score was 27 (range 25-30).

**CVVHDF conditions**

The actual flow rates achieved were recorded and compared with the target flow rates. The mean effluent flow rate achieved was 3.35 +/- 0.50 L/hr (Range: 2.9 - 4.0 L/hr). The mean duration of CVVHDF therapy was 9.3 +/- 3.7 days. The mean number of filters used per dosage interval was 1.1. The mean duration of use of a filter was 50.6 hours.

**Pharmacokinetic profiles**

Seventeen pharmacokinetic profiles were obtained from these seven patients. The ciprofloxacin pharmacokinetic
parameters estimated from each patient’s pharmacokinetic profile, during treatment with CVVHDF are presented in Table 2. Ciprofloxacin $t_{1/2}$ during CVVHDF was variable, ranging from 5.15 to 39.4 hours, with a median of 13.8 hours, reflecting a median elimination rate constant of 0.050 (range 0.018-0.135) hr$^{-1}$. The average $t_{1/2}$ of patients 1 and 4 (both with hepatic impairment) were 37.3 and 25.9 hours, respectively. These $t_{1/2}$ values are seven to eight times that obtained in patients with normal renal function, and were the highest obtained in the current study. Patient 4 had evidence of liver injury that may have resulted in impaired

Table 1 Demographic and clinical data of patients on continuous veno-venous haemodiafiltration administered ciprofloxacin

| Sex | Age | Diagnosis                                                                 | Infective pathogen       | APACHE II score (initial/highest) | CVVHDF Duration(days) | ICU Mortality | Outcome |
|-----|-----|---------------------------------------------------------------------------|--------------------------|-----------------------------------|------------------------|---------------|---------|
| M   | 60  | Intestinal Obstruction, Hemicolecotomy                                    | Escherichia coli         | 26                                 | 6                      |              | Survived |
| F   | 77  | Neutropaenic sepsis                                                       | Pseudomonas aeruginosa   | 27                                 | 5                      |              | Died     |
| F   | 68  | Intestinal obstruction, post-operative sepsis and acute renal failure    | Pseudomonas aeruginosa   | 28                                 | 14                     |              | Survived |
| M   | 47  | Acute pancreatitis, sepsis                                               | Escherichia Collia       | 25                                 | 14                     |              | Survived |
| F   | 71  | ESRD with severe sepsis                                                   | Empiric cover            | 27                                 | 8                      |              | Died     |
| M   | 57  | Hepatic cirrhosis with severe sepsis                                      | Pseudomonas Aeruginosa, Enterococcus faecalis | 29                                 | 7                      |              | Survived |
| M   | 28  | Acute liver failure with severe sepsis                                    | Pseudomonas aeruginosa   | 30                                 | 11                     |              | Survived |

Table 2 Estimates of pharmacokinetic parameters obtained from multiple ciprofloxacin serum concentrations in a dosage interval using non-compartmental methods

| Patient Profile | Dose (mg) | Dosage Interval (hours) | $T_{1/2}$ (hrs) | $k$ (hr$^{-1}$) | $\text{AUC}_{0-\tau}^*$ (mg.hr/L) | TBC (Dose/AUC) (L/hr) | Vdss (L) |
|-----------------|-----------|-------------------------|-----------------|----------------|----------------------------------|-----------------------|----------|
| 1.A             | 400       | 12                      | 35.2            | 0.020          | 35.4                             | 11.3                  | 524      |
| 1.B             | 400       | 12                      | 39.4            | 0.018          | 38.3                             | 10.4                  | 555      |
| Mean            |           |                         | 37.3            | 0.019          | 36.8                             | 10.9                  | 539      |
| 2.A             | 200       | 12                      | 5.15            | 0.135          | 15.2                             | 13.2                  | 104      |
| 2.B             | 200       | 12                      | 13.8            | 0.050          | 16.5                             | 12.2                  | 215      |
| 2.C             | 400       | 12                      | 12.4            | 0.056          | 51.8                             | 7.72                  |          |
| Mean            |           |                         | 10.5            | 0.080          | 39.5                             | 10.1                  | 88.4     |
| 3.A             | 400       | 12                      | 5.97            | 0.116          | 38.9                             | 10.3                  | 79.5     |
| 3.B             | 400       | 12                      | 7.50            | 0.092          | 40.2                             | 10.0                  | 97.3     |
| Mean            |           |                         | 6.73            | 0.104          | 39.5                             | 10.1                  | 88.4     |
| 4.A             | 400       | 24                      | 24.7            | 0.028          | 129                              | 3.10                  | 111      |
| 4.B             | 400       | 12                      | 27.2            | 0.026          | 81.5                             | 4.91                  |          |
| Mean            |           |                         | 25.9            | 0.027          | 4.00                             |                       |          |
| 5.A             | 400       | 12                      | 8.44            | 0.082          | 40.4                             | 9.90                  | 107      |
| 5.B             | 400       | 12                      | 5.77            | 0.120          | 37.8                             | 10.6                  | 81.1     |
| 5.C             | 400       | 12                      | 6.80            | 0.102          | 40.9                             | 9.78                  | 88.2     |
| Mean            |           |                         | 7.00            | 0.101          | 39.7                             | 10.1                  | 92.2     |
| 6.A             | 400       | 24                      | 14.0            | 0.050          | 43.4                             | 9.22                  | 175      |
| 6.B             | 400       | 12                      | 14.7            | 0.047          | 54.0                             | 7.40                  | 151      |
| 6.C             | 400       | 12                      | 16.5            | 0.042          | 49.6                             | 8.06                  |          |
| Mean            |           |                         | 15.0            | 0.046          | 8.23                             | 163                   |          |
| 7.A             | 400       | 24                      | 15.1            | 0.046          | 50.6                             | 7.91                  | 164      |
| 7.B             | 400       | 12                      | 10.4            | 0.067          | 39.4                             | 10.1                  | 139      |
| Mean            |           |                         | 12.7            | 0.056          | 9.00                             | 151                   |          |

* $\tau$ taken to be 24 hours for first profile immediately following a change in prescribed dosage interval (profiles 6b and 7b)
biliary clearance, and patient 1 had concurrent alcoholic liver disease, which may have contributed to the prolonged t1/2. In patient 4, profile 4a, the clearance was calculated using the estimated AUC0-∞, as this profile was measured following the initial dose. The long half life calculated (25 h) in combination with the lower volume of distribution lead to a comparatively low estimated TBC. The t1/2 observed in patients 3 and 5, 6.73 and 7.00 respectively, were closer to those seen in patients with normal renal function. The median TBC of ciprofloxacin was 9.90 (range 3.10-13.2) L/hr (~0.14 L/hr/kg based on a 70 kg patient). This value represents hepatic, residual renal and transintestinal ciprofloxacin clearance, in addition to ciprofloxacin clearance by the filter. The Vdss for ciprofloxacin during CVVHDF therapy ranged from 79.5-555 L with a median of Vdss of 125 L. The mean Cpmax concentration following administration of 400 mg every 12 hours was 5.8 +/- 1.0 mg/L.

The clearances of ciprofloxacin and creatinine by CVVHDF are presented in Table 3. The mean clearance of ciprofloxacin by CVVHDF was 2.47 +/- 0.29 L/hr, thus the clearance of ciprofloxacin by CVVHDF was on average 26% of the TBC, reflected in the mean FCVVHDF of 0.26 (Table 3). This value excludes that of patient 4. In this case a significant fraction (0.74) of the clearance is calculated to have occurred via CVVHDF, and was therefore considered an atypical value.

The Scipro was 0.70 +/- 0.06. A simple method for estimating drug clearance through the filter, without measuring drug levels, involves using the non-protein bound fraction (fu) of ciprofloxacin as an estimate of the sieving coefficient, as it is the unbound fraction that crosses the filter. Hoffken et al [23] and Joos et al [24] have reported fu values for ciprofloxacin of 0.6 and 0.78 respectively. Applying these values to the observed flow rates in this study gives clearance estimates of 2.0 L/hr and 2.7 L/hr, which approximate the measured value of 2.47 L/hr. The sieving coefficient for creatinine (0.82 +/- 0.04) was quite similar to that estimated for ciprofloxacin. A correlation between ciprofloxacin clearance due to CVVHDF (y) and creatinine clearance by the filter (x) was observed (y = -0.29 + 1.03x, r² = 0.76) and is illustrated in Figure 1. Ciprofloxacin and creatinine clearances over time were examined in order to identify any change in filter efficiency over time. There was little variation in filter performance as the clearance of both creatinine and ciprofloxacin remaining relatively constant.

Within the observed range of effluent flow rates and CVVHDF ciprofloxacin clearance rates in the current study, there is a suggested trend (r² = 0.94) of increasing ciprofloxacin clearance with higher effluent fluid flow rates, which is illustrated in Figure 2.

**Pharmacokinetic - Pharmacodynamic parameters**

The PK-PD parameters, Cmax/MIC ratios and the ratio of AUC0-24 /MIC, achieved with a ciprofloxacin dosing regimen of 400 mg ciprofloxacin every 12 hours are summarised in Table 4.

The median AUC0-24/MIC ratio for patients administered Ciprofloxacin 400 mg twice daily was 161. An AUC0-24/MIC~ > 100 has been propounded as an indicator of adequate ciprofloxacin dosing [12].

**Discussion**

The pharmacokinetic parameter estimates obtained, half life [median 13.8 (range 5.15-39.4) hours], TBC [median 9.90 (range 3.10-13.2) L/hr] and median Vdss of 125 (range 79.5-555) L illustrate the high level of interpatient variability in ciprofloxacin disposition in critically ill patients during CVVHDF. The t1/2 of ciprofloxacin, approximately 4 hours in patients with normal renal function, doubles in patients with severe renal impairment. In general, accumulation will not be observed with 12 hour dosing as this interval is greater than the half-life, in patients without liver dysfunction. As significant accumulation was observed with an interval of eight hours in previous studies [15,17,25] a longer dosage interval of 12 hours for patients on CVVHDF should therefore be considered. Patients 1,4,6 and 7 had

### Table 3 Ciprofloxacin and Creatinine Clearance by continuous veno-venous haemodialfiltration.

| Patient | ClCVVHDF (L/hr) | ClCREAT (L/hr) | FCVVHDF | Measured effluent fluid rate (L/hr) | Total Body Clearance (L/hr) |
|---------|----------------|----------------|---------|-----------------------------------|---------------------------|
| 1 A     | 2.8            | 2.9            | 0.25    | 4.0                               | 11.3                      |
| 2 C     | 2.4            | 2.6            | 0.31    | 3.4                               | 7.72                      |
| 3 B     | 2.7            | 2.9            | 0.27    | 3.9                               | 9.96                      |
| 4 A     | 2.3            | 2.3            | 0.27    | 2.9                               | 3.10                      |
| 5 A     | 2.2            | 2.6            | 0.22    | 3.0                               | 9.90                      |
| 6 C     | 2.1            | 2.4            | 0.26    | 2.9                               | 8.06                      |
| 7 B     | 2.8            | 2.9            | 0.28    | 4.0                               | 10.1                      |

Mean +/- SD 2.47 +/- 0.29 2.66 +/- 0.25 0.26 ± 0.03* 3.35 +/- 0.50 8.60 ± 2.7

* Excluding value from patient 4A
average half-lives varying from 13-15 hours (patients 6 and 7) to greater than 25 hours (patients 1 and 4), demonstrating the variability of pharmacokinetic profiles in this patient group, and also likely reflecting decreased hepatic clearance in these four patients.

Wallis et al [15] reported a similarly reduced ciprofloxacin clearance in six patients with renal failure, treated with 200 mg ciprofloxacin three times daily during CVVHDF therapy (0.06-0.25 L/hr/kg).

The median volume of distribution of 125 L (mean 185 +/- 155) is similar to values reported by Wallis et al [15] (mean: 135 +/- 27 L) estimated from six patients treated with 200 mg every 8 hours and by Lipman et al [18] (range: 0.77 - 2.52 L/kg) for critically ill patients. The current patient sample showed greater variability: Patient 1, in particular, had a very high Vdss of 539L. The average Vdss for the other 6 patients was 126 +/- 43L. These values compare well with those detailed above from Wallis et al [15], and probably reflect more typical Vdss values of ciprofloxacin in this patient population. However, the high Vdss calculated from patient 1 serves as evidence of the unpredictable drug disposition which can occur in critically ill patients, reflecting greater degrees of capillary leak in keeping with the severity of illness.

A practical and useful finding was that, within the range studied, creatinine clearance may serve as a clinical surrogate for ciprofloxacin clearance on CVVHDF. This relationship is clinically important as ciprofloxacin is not routinely assayed in most hospitals. The relationship did not decline over the life of the filter. This relationship may serve as a useful guide to dosing ciprofloxacin within this range of creatinine clearance values.

As effluent flow rates increased, there was a suggested trend of increased ciprofloxacin clearance via CVVHDF. However, there was no observed change in TBC with increasing effluent flow rate. This illustrates the varying role of compensatory and alternative elimination methods such as hepatic elimination. Further studies on this association between effluent flow rate and ciprofloxacin clearance via CVVHDF to investigate the presence of a cause-effect relationship would be beneficial and may helpfully influence dosing decisions. This is of importance in particular as increased effluent flow rates may be used for purposes other than enhancing drug clearance, and therefore TBC in such patients can be difficult to estimate in the absence of plasma concentration data and due to the varying influence of alternative elimination routes. Further insight into the effect of increasing effluent flow rate on clearance via CVVHDF is therefore desirable. Prospectively, such dosing considerations are often hampered by the discrepancy between prescribed and achieved flow rates.

CVVHDF was responsible for clearing approximately one quarter of all ciprofloxacin eliminated. Its relative contribution to ciprofloxacin TBC will be greatest in patients with concurrent hepatic and renal dysfunction,
as in these patients, CVVHDF will become a proportionately more significant route. Therefore care is required in dosing patients with concurrent renal and hepatic failure/impairment to avoid accumulation of ciprofloxacin. Interestingly, clearance of ciprofloxacin via CVVH of up to 25% has been reported [21], which is similar to that observed in the current study using CVVHDF. This implies that both dialysis parameters and patient specific parameters have a role to play in the observed variability in clearance via CRRT, in addition to the CRRT method used.

There is now significant evidence that correct and timely antibiotic choices will save more lives than virtually all other ICU therapies [4,26]. A \( C_{\text{pmax}} / \text{MIC} \) ratio of \( \sim 10 \) has been suggested [9,11] as desirable and thus a 400 mg twice daily regimen appears to achieve these target concentrations during CVVHDF therapy (Table 4). 200 mg twice daily being inadequate. For ciprofloxacin, the median \( C_{\text{pmax}} \) achieved in this study was 5.2 (range 5.0-7.3) mg/L (mean 5.8 \( \pm \) 1.0 mg/L), which represented a median \( C_{\text{pmax}} / \text{MIC} \) ratio (based on an MIC of 0.5 mg/L) of 10.3. The median \( \text{AUC}_{0-24} \) was 80.4 (range 70.8-104) mg.hr/L (mean 83.0 \( \pm \) 11.1 mg.hr/L), which corresponds to a median \( \text{AUC}_{0-24} / \text{MIC} \) ratio of 161 (range 142-207). A suggested characteristic of adequate dosing for ciprofloxacin is an \( \text{AUC}_{0-24} / \text{MIC} \) ratio \( > 100 \).

Wallis et al [15] reported lower \( C_{\text{pmax}} \) concentrations and \( \text{AUC}_{0-24} \) values with a lower daily dose of 600 mg ciprofloxacin, compared to the 800 mg daily dose used in this study. The CVVHDF conditions in our study were similar to those reported by Wallis et al [15]. Wallis et al [15] used a dosing schedule of 200 mg every 8 hours and the mean \( C_{\text{pmax}} \) concentration was 3.5 \( \pm \) 0.5 mg/L. This dosing schedule achieves on average a \( C_{\text{pmax}} / \text{MIC} \) ratio of 7 (based on a MIC of 0.5 mg/L). The mean \( \text{AUC}_{0-24} \) achieved by the same dosing schedule of 200 mg every 8 hours was 48.3 \( \pm \) 8.7 mg.hr/L, equivalent to a \( \text{AUC}_{0-24} / \text{MIC} \) ratio of 96.6 \( \pm \) 17.4, on the basis of a MIC value of 0.5 mg/L. Malone et al [27] reported a mean \( C_{\text{pmax}} \) of 3.9 mg/L (\( C_{\text{pmax}} / \text{MIC} \) ratio; 7.8) for three patients treated with 400 mg ciprofloxacin every 24 hours during CVVHDF therapy. The mean \( \text{AUC}_{0-24} \) with this dosing schedule was 56.8 mg.hr/L, which represents an \( \text{AUC}_{0-24} / \text{MIC} \) ratio of 114 (assuming an MIC of 0.5 mg/L). The CVVHDF conditions employed by Malone et al [27] were different from those used in the current work.

On the basis of these pharmacodynamic considerations, the dosing schedule utilised in this study gives better cover than previously studied dosage strategies and should serve as a pharmacokinetically and pharmacodynamically valid dose guide in the appropriate clinical circumstances.

One limitation of this work is common to all carried out in this field, that patient numbers are small, and as such the conclusions that can be drawn are limited to a very narrow patient cohort. A consideration for future research might be that a randomised crossover design could be employed to add further clarity to dosing recommendations. As both antimicrobial doses, and dialysis parameters such as flow rate, are frequently adjusted on the basis of changing clinical need in the intensive care setting, there are ethical difficulties surrounding the set up and design of such trials.

Another limitation was that liver dysfunction or impairment was not characterised in a standardised manner. However this is difficult in these patients due to blood product and vitamin K administration, particularly in septic and coagulopathic patients and also because of concurrent hepatotoxic drug administration. Similarly, the varying nature from day to day of hepatic/renal function in many critically ill patients suggest that calculations based on steady state be interpreted with caution, as clearance is likely to be variable. Furthermore, it is extremely difficult to quantify any residual renal function, and thereby contribution to the clearance, that these patients made have had.

**Conclusion**

Our results suggest that a dose rate of 400 mg every 12 hours, will achieve the recommended PK-PD goals in most patients on CVVHDF. Twice daily dosing of ciprofloxacin maximised peak concentrations, while minimising accumulation. Concomitant hepatic and renal dysfunction results in a prolonged elimination half-life. Creatinine clearance by the filter may be used to estimate ciprofloxacin clearance by CVVHDF (within the range studied). Thus in the absence of ciprofloxacin plasma levels, creatinine clearance by the filter could be considered as a surrogate marker for ciprofloxacin clearance in patients, this may be particularly useful when other routes of elimination are impaired.

The data suggest that drug clearance increases with increasing effluent flow rate, which in turn may require even higher ciprofloxacin dosing. This association between effluent flow rate and drug clearance requires further elucidation to determine the nature of any cause-effect relationship.

While a 400 mg dose administered at 12 hourly intervals achieved adequate \( C_{\text{pmax}} \) concentrations and lower doses may result in target serum concentrations in some patients with hepatic dysfunction, given the general emergence of ciprofloxacin resistance and the wide therapeutic index of ciprofloxacin, it may be advisable to maintain the higher ciprofloxacin dose as the mainstay of therapy. The possibility of accumulation in patients where more than one elimination route is impaired
should be considered and this can be addressed by extension of the dosage interval.

Key Messages

- Ciprofloxacin 400 mg twice daily IV will achieve the recommended PK-PD goal (AUC0-24/MIC ratio >125) in most patients on CVVHDF.
- Concomitant hepatic and renal impairments results in a prolonged ciprofloxacin elimination half life, therefore dosage interval extension may be required.
- Creatinine clearance by the filter correlates well with ciprofloxacin clearance by the filter, therefore creatinine clearance by the filter (in the range studied) may be used as a surrogate for ciprofloxacin clearance.

List of abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation score; AUC: Area Under the Curve; AUMC: Area Under the Moment Curve; CI: Confidence Interval; Clcr: Clearance of creatinine; Cmax: Maximum plasma concentration; Crmeas: Creatinine concentration; CRRT: Continuous Renal Replacement Therapy; CVVHDF: Continuous Veno-Venous Haemodialfiltration; ESRD: End Stage Renal Disease; fCVVHDF: Fraction cleared by continuous veno-venous haemodialfiltration; fP: Non protein bound fraction; HPLC: High Performance Liquid Chromatography; ICU: Intensive Care Unit; LFTs: Liver Function Tests; MIC: Minimum Inhibitory Concentration; PK-PD: Pharmacokinetic - Pharmacodynamic; Q: Effluent flow rate; S: Sieving coefficient; t1/2: Half life; TBC: Total Body Clearance; tinf: Infusion duration time; V: Volume of distribution; Vmeas: Volume of distribution at steady state; λ: First order elimination rate constant; τ: Dosage interval.

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The views expressed in this article are the personal views of the author(s).

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Authors’ contributions

OC, CG, MD and AS initiated and supervised the study from its inception. CD devised study protocols and completed clinical trial applications. AS and CD co-ordinated sample acquisition. AS undertook sample analysis under the supervision of OC. AS and DD completed the pharmacokinetic analysis and modelling. AS and OC authored the first draft, with review and additions by DD, MD and CG. AS, OC, CG, MD, CD and DD read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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