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Pharmacokinetics of Piperacillin and Ciprofloxacin in Critically Ill Patients Undergoing Continuous Venovenous Haemodialysis or Haemodiafiltration

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Abstract

In sepsis an early time point of administration, adequate choice of an antibiotic drug and correct dosage are crucial for survival. Acute renal failure in severe sepsis can be treated by continuous renal replacement therapy but interferes with the pharmacokinetics of antibiotic drugs. The aim of the present study was to investigate the efficacy and safety of an antibiotic therapy with piperacillin/tazobactam and ciprofloxacin.

In a single-center, prospective, open-label study a total of 24 patients with acute renal failure treated with continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF) were enrolled in a clinical trial. Serum concentrations (C_{max}, C_{min}) and pharmacokinetic parameters of piperacillin and ciprofloxacin were analyzed. Optimum exposure to piperacillin is expected when serum concentrations are maintained 4-5 times higher than the minimum inhibitory concentration (MIC), i.e. above 64 mg/l. Optimum exposure to ciprofloxacin is given when the ratio (AUIC) of AUC and MIC is ≥ 125 h per dosing interval. In addition the C_{max}/MIC ratio should amount to ≥ 10.

Plasma concentrations lower than 64 mg/l were determined in 10 out of 21 patients treated with piperacillin. Nine out of 20 patients treated with ciprofloxacin had a calculated AUIC ≥ 125 h and a C_{max}/MIC ratio ≥ 10.

In critically ill patients undergoing CVVD or CVVDF piperacillin/tazobactam dosing should be increased to 4/0.5 g four times daily and ciprofloxacin dosing to 400 mg twice daily. Therapeutic drug monitoring of antibiotic therapies would be reasonable in these patients.

The trial is registered at clinicaltrialsregister.eu ID: 2010-021369-66.

Keywords: Continuous haemodialysis; Piperacillin/tazobactam; Ciprofloxacin; Critically ill patients; Sepsis

Introduction

Critically ill intensive care patients are frequently suffering from sepsis and multi organ failure associated with a high mortality rate [1-3]. Diagnosis of severe sepsis or septic shock requires immediate administration of anti-infective medication because the mortality rate increases with delayed anti-infective therapy. The initial empiric antibacterial therapy comprises one or more antibiotics that are effective against all likely pathogens causing the infection [4]. Piperacillin/tazobactam, a time dependent antibiotic, and ciprofloxacin, a concentration dependent antimicrobial agent, are often used for empiric therapy. While time dependent antibiotics should reach concentrations higher than four times of the minimal inhibition concentration (MIC) of the pathogen, a high ratio of the area under the curve (AUC) to MIC is important for concentration dependent drugs like quinolones [5-8]. The appropriate dosing is crucial for the patients' outcome. While too low antibiotic concentrations can lead to treatment failures and induce bacteria resistance, too high concentrations can increase side effects and may lead to unnecessary consumption of health care resources. Pharmacokinetic and pharmacodynamic behavior of the antibiotic drugs is affected by acute renal failure (ARF) and by continuous renal replacement therapy (CRRT) [9].

Continuous venovenous haemodialysis (CVVHD) and continuous venovenous haemodiafiltration (CVVHDF) are frequently chosen modes of CRRT in patients suffering from severe sepsis including ARF. The diffusion based dialysis in CVVHD and CVVHDF eliminates antibiotic drugs more effectively than convection based dialysis methods like continuous venovenous haemofiltration (CVVH) [10-12]. However these extracorporeal clearance procedures are known to be associated with potential underdosing of the antibiotic drug therapy [13]. The elimination rate of the drugs depends on the physicochemical nature and pharmacokinetic behavior of the antibiotic compound as well as the specific dialysis method and its operating conditions used. Hydrophilic antibiotic drug substances (e.g. β-lactams) are usually distributed in a limited space and excreted via the renal route as unchanged drugs, whereas lipophilic substances (e.g. fluoroquinolones) are widely distributed into the intracellular space and often hepatically metabolized prior to renal elimination [14]. In acute sepsis the volume of distribution is known to increase significantly because of capillary leakage which might lead to unpredictable pharmacokinetic behavior [7]. With regard to the CRRT method, the extent of drug removal is expected to correlate with the type and surface area of the filter membrane and the rate of the dialysate solution. In addition,

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elimination of the drug substances varies according to the patients' residual renal function.

In order to avoid under- or overdosage of antibiotics therapeutic drug monitoring (TDM) is highly recommended in intensive care patients undergoing CRRT [15,16]. TDM is based on the measurement of antimicrobial drug concentrations in the biological matrices using analytical methods like high performance liquid chromatography (HPLC) coupled with ultraviolet detection or mass spectrometry. In order to study the pharmacokinetics of the specified antibiotics a new HPLC method in combination with solid phase extraction (SPE) for the simultaneous determination of piperacillin and ciprofloxacin was developed and validated [17]. The implementation of the analytical method was a prerogative and part of the clinical study described here. The aim of the study was to investigate the pharmacokinetics of piperacillin/tazobactam and ciprofloxacin in critically ill intensive care patients undergoing CVVHD or CVVHDF under defined operating conditions. Primary endpoint was the rate of sub therapeutic antibiotic exposure in these patients determined.

Materials and Methods

Study design and population

A single-centre, prospective, open-label study protocol for critically ill intensive care patients treated with CVVHD or CVVHDF and empiric antibiotic therapy was designed. Adult intensive care unit (ICU) patients (age>18 years) suffering from severe sepsis and the consecutive clinical need for an antibiotic treatment with piperacillin/tazobactam and/or ciprofloxacin and suffering from ARF with the need for CRRT were eligible for the study. Written consent for the study was given by the patient or his legal surrogate. Patients who were included in other clinical trials were not eligible.

The study was conducted at the University Medical Center Mainz, Germany and approved by the Ethics Committee (Institutional Review Board (IRB) of the Federal State of Rhineland-Palatinate, Germany (IRB approval number: 837.250.10, September 2010). Clinical trial approval was granted by the national approval authority Federal Institute for Drugs and Medical Devices (EudraCT Number 2010-021369-66). The study was performed according to The Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from the legal surrogates of all patients. 24 patients were enrolled over a period of 12 months. CVVHD and CVVHDF (multiFiltrate-syteme, Fresenius Medical care, Germany) were performed using a polysulfone high-flux dialyzer (1.8 m^2) (Ultraflux AV 1000 S). Upper and lower limits set were 100-150 ml/min for blood flow and 2-2.4 l/h for dialysate flow. During CVVHDF limits set for flow of the substituate solution were 700-800 ml/h. The ultrafiltrate flow varied depending on the patients' renal function. In addition to the local citrate anticoagulation, systemic anticoagulation was performed with dalteparin, enoxaparin, heparin or argatroban according to the individual needs of the patients.

Dosing and sampling of piperacillin and ciprofloxacin

In general piperacillin/tazobactam 4/0.5 g was administered three times per day and ciprofloxacin 200 mg was administered twice per day in the critically ill patients undergoing CRRT. Due to a broad pharmacokinetic and pharmacodynamic variability dosage of antibiotics in continuous renal replacement therapy is challenging. The dosage of piperacillin/tazobactam and ciprofloxacin has been derived from several studies [18-27]. Piperacillin is a hydrophilic antibiotic with an average distribution volume in steady state (VdSS) of about 21 ± 5,5 L [28,29]. Hence a dose adaptation for obesity is not required. Plasma and dialysate concentrations of piperacillin and ciprofloxacin were measured in the steady state treatment phase (day three after start of antibiotic therapy). Blood samples were collected immediately before and after administration of the antibiotic drug solution and up to a 12 hour interval. During this interval dialysate samples were withdrawn whenever the filtrate bags were exchanged. Serum and dialysate concentrations (C_{max}, C_{min}) of piperacillin and ciprofloxacin were analyzed by a previously published validated HPLC method combined with solid phase extraction for plasma samples [17]. The method was developed for the simultaneous analysis of piperacillin and ciprofloxacin in serum and dialysate samples. Method validation was performed according to the Guideline of the European Medicines Agency on validation of bioanalytical methods.

Pharmacokinetic data analysis

The resulting concentrations were used to calculate the pharmacokinetic parameters of piperacillin and ciprofloxacin i.e. half time ($t_{0.5}$), distribution volume in the steady state (Vd_{SS}), area under the curve (AUC), area under the first moment curve (AUMC), total clearance (Cl_{total}), dialysate clearance (Cl_{CRRT}) and extrarenal clearance ($Cl_{extrarenal}$). $Cl_{extrarenal}$ was calculated as difference between Cl_{total} and Cl_{CRRT} (excreted amount of piperacillin and ciprofloxacin in dialysate divided by the AUC of the collecting interval). Concentration time curves were calculated and plotted using Microsoft Excel. Statistical analysis was performed using SPSS version 20 (IBM, Ehningen, Germany). Optimum exposure to piperacillin is expected when serum concentrations are maintained 4-5 times higher than the minimal inhibitory concentration (MIC), i.e. above 64 mg/l over the complete dosing interval. Optimum exposure to ciprofloxacin is expected when the ratio (AUIC) of the area under the curve (AUC) and MIC is ≥ 125 h and the C_{max}/MIC ratio amounts to ≥ 10 per dosing interval.

Statistical analysis was planned in cooperation with the Institute of Medical Biometry, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Germany. For each antibiotic (piperacillin and ciprofloxacin) 20 patients were planned to take part in the clinical trial. As primary endpoint the rate of subtherapeutic antibiotic exposure in the patient group was chosen. A t-test was performed for piperacillin (MIC>64 mg/l after 8 h; n=20; α=5%) and ciprofloxacin (AUIC>125 h; n=20; α=5%). The binomial distribution of the sample was tested. The null hypothesis determined for piperacillin were plasma concentrations <64 mg/l after an interval of 8 hours and for ciprofloxacin an AUIC<125 h. With the method of Pearson and Clopper the upper and lower limit of confidence intervals were calculated. The calculated confidence intervals represent 95% probability of underdosing in the study population.

Results

Patient characteristics

Over a period of twelve months 24 patients were included in the clinical trial. 21 patients were treated with piperacillin/tazobactam and 20 patients were treated with ciprofloxacin. Only 7 patients were treated with monotherapy. The patient demographic data and clinical information are given in Table 1. Most patients were suffering from septic shock associated with acute renal failure. Five patients also suffered from liver cirrhosis or liver failure. The mean Apache II score was 29 ± 7.5, the mean TISS 28 Score was 39 ± 6.8. Nine of the 24 (17 male, 7 female) patients enrolled, died during their stay on the ICU. 21 patients were treated with CVVHD, 3 patients were treated with

Patient [No.]	Age [years]	Height [cm]	Weight [kg]	Gender[a]	Diagnosis	AP II[b]	Tiss 28[c]	Outcome
1	72	185	90	M	Sepsis, ARDS[d]	45	45	Died
2	75	163	75	M	SIRS[e]	29	38	Discharged
3	75	170	75	M	Pneumonia	42	43	Discharged
4	77	170	95	M	Hemorrhagic shock	24	26	Discharged
5	78	172	120	M	Hemorrhagic shock	32	41	Discharged
6	53	172	105	M	Pneumonia, Sepsis	27	32	Discharged
7	70	178	50	M	Sepsis, Pneumonia	21	41	Died
8	56	157	50	F	Sepsis	24	37	Died
9	53	180	140	M	SIRS,	23	39	Died
10	58	175	69	M	Sepsis,	16	36	Discharged
11	60	160	45	F	Sepsis	30	39	Discharged
12	70	178	95	M	Sepsis	29	59	Discharged
13	48	190	104	M	Liver dysfunction, SIRS[e]	28	39	Discharged
14	60	179	70	F	Sepsis	19	35	Discharged
15	61	174	105	M	Sepsis	21	35	Discharged
16	75	157	64	F	Sepsis	29	42	Discharged
17	28	172	80	M	Sepsis	22	33	Discharged
18	68	160	80	F	Sepsis, ARDS[d]	28	31	Died
19	54	170	120	F	Sepsis	42	45	Died
20	76	180	90	M	Sepsis	30	35	Discharged
21	50	185	150	M	Fournier- gangrene	26	36	Died
22	65	175	100	M	SIRS[e]	34	50	Discharged
23	69	172	106	M	ARDS[d]	39	32	Died
24	73	156	59	F	SIRS	33	40	Died
Mean	64	172	89			29	39	
SD	12	9	27			7.5	6.8	

[a] m/f = male/female

[b] Apache Score = Acute Physiology And Chronic Health Evaluation Score

[c] TISS 28 = Therapeutic Intervention Scoring System

[d] ARDS = Acute Respiratory Distress Syndrome

[e] SIRS = Systemic Inflammatory Response Syndrome (initial suspicion of sepsis)

Table 1: Demographic and clinical data of the study population.

CVVHDF. During CVVHD blood flows varied between 100-120 ml/min and dialysate flows between 2-2.2 l/h. During CVVHDF blood flow was increased up to 150 ml/min, flow of the dialysate solution varied between 1.3 and 2.6 l/h. The flow of the substituate solution amounted to 0.7-0.8 l/h. The ultrafiltration rate was kept between 100-450 ml/h. Except one patient, all patients lost their urine production completely.

Pharmacokinetic profiles of piperacillin were assessed in 21 patients during treatment with piperacillin/tazobactam 4.0/0.5 g three times a day (Figure 1). On average the C_{max} and C_{min} concentrations amounted to 249 mg/l and 54 mg/l, respectively. The mean Vd_{ss} was calculated to be 25 l with a mean Cl_{total} of 94 ml/min. The resulting $t_{0.5}$ amounted to 7.6 h.

Pharmacokinetic profiles of ciprofloxacin were assessed in 20 patients during treatment with ciprofloxacin 20 0 mg twice a day (Figure 2). The mean C_{max} and C_{min} concentrations amounted to 5.2 mg/l and 1.6 mg/l respectively. The mean Vd_{ss} was 66 l with a mean Cl_{total} of 154 ml/min and $t_{0.5}$ of 20 h.

The mean Cl_{CRRT} was similar for piperacillin (27 ml/min) and ciprofloxacin (24 ml/min). However the $Cl_{extrarenal}$ was much higher for ciprofloxacin (129 ± 107 ml/min) than for piperacillin (67 ± 48 ml/min). Related to the Cl_{total}, 29% of piperacillin and 16% of ciprofloxacin were eliminated by CRRT. Despite the moderate rate of Cl_{CRRT} the exposure of the patients to piperacillin and ciprofloxacin revealed to be inadequate.

At the end of the eight hour dosing interval in 10 out of 21 patients, plasma concentrations of piperacillin fell below 64 mg/l (Figure 3).

The t-test was performed for 20 patients treated with piperacillin and 19 patients treated with ciprofloxacin. Plasma concentrations were not significantly higher than the MIC of 64 mg/l or the AUIC of 125 h according to the one sided t-test. Ten out of 21 patients treated with piperacillin were underdosed. Nine out of 20 patients treated with ciprofloxacin were underdosed (Table 2).

According to the Pearson-Clopper test 26-70% of the patients treated with piperacillin and 29-76% of the patients treated with ciprofloxacin were underdosed. Plasma concentrations of both antibiotics were lower than the target concentrations associated with optimal antibiotic efficacy.

Discussion

Pharmacokinetics of antibiotics can be altered intensely in critically ill patients especially when they undergo CRRT. Loss of organ function like ARF influences the excretion of the drugs. Furthermore in patients exposed to CRRT excretion is altered by the type of CRRT, dialysate and blood flow as well as the ultrafiltration rate.

Out of 24 patients included in the clinical study, 21 patients received piperacillin/tazobactam and 20 patients received ciprofloxacin. 17 patients received both antibiotics as a combination therapy. The sample size of patients is higher than in other published studies

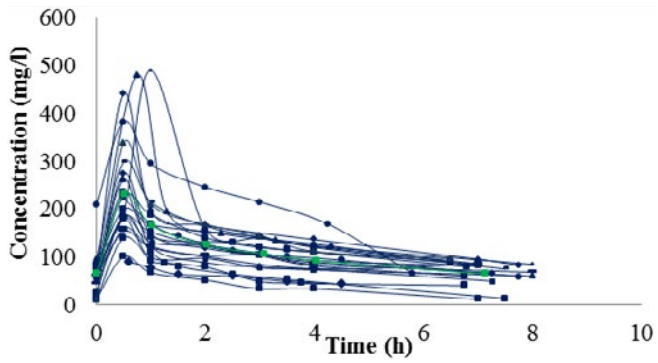

Figure 1: Individual (blue) and mean (green) plasma concentration curves of patients treated with piperacillin.

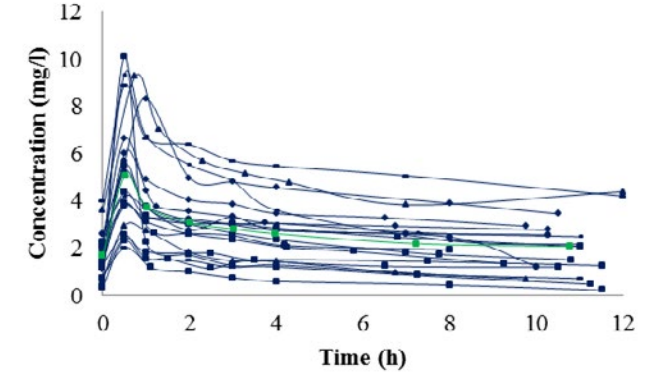

Figure 2: Individual (blue) and mean (green) plasma concentration curves of patients treated with ciprofloxacin.

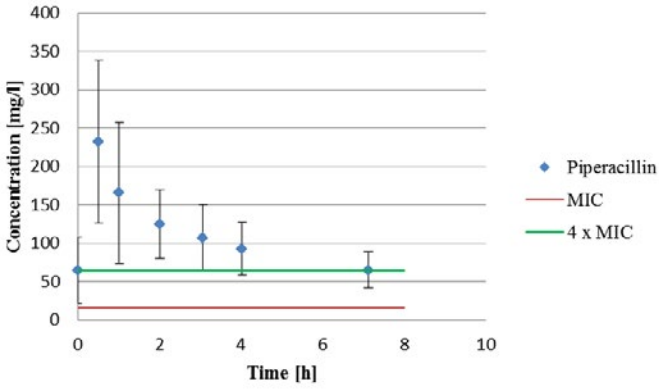

Figure 3: Concentration time curve of mean ± SD piperacillin concentrations in 21 patients. Optimum exposure to piperacillin is expected when serum concentrations are maintained 4-5 times higher than the minimum inhibitory concentration (MIC), i.e. above 64 mg/l.

[18-22,26,30] and underscores the validity of the study results. Of note the study population is homogenous with regard to antibiotic treatment, renal function, and type and conditions of CRRT. The mean Apache II score (29 ± 7.5 points) of the study population is comparable to those enrolled in other studies [19,21,27] or even higher [24,30]. Nearly all patients lost their urine production completely and underwent continuous hemodialysis procedures. According to the study protocol pharmacokinetic data of the three patients treated with CVVHDF were evaluated together with the 21 patients treated with CVVHD. Differences in the pharmacokinetics of the antibiotics were not observed. Conditions of CVVHD (blood flow 100-150 ml/min; dialysate flow 2-2.4 l/h) were similar in all patients included in the study. Fluid balance was regulated by ultrafiltration. The resulting blood flow was comparable to those used in other studies [18-24,27,30,31] while the surface of the inserted polysulfone filters (1.8 m^2) was considerably larger than in other studies (0.5-0.7 m^2) [18,20,26].

Piperacillin/tazobactam

Today it is well accepted that concentrations of time dependent antibiotics should remain in critically ill patients four times higher than the MIC [5,32,33] over the complete dosing interval [5,6]. However in clinical practice standard doses are used to start empiric antibiotic therapy. According to the product information and published results [15,30,34] in this pharmacokinetic study piperacillin/tazobactam 4.0 g/0.5 g was infused three times daily. Because of the wide therapeutic index of tazobactam plasma concentrations were not analyzed. Only one study reports an accumulation of tazobactam [21].

Only 11 out of 21 patients reached the target plasma levels on day 3 of piperacillin therapy. The fact that 26-70% of the included patients were underdosed corresponds to other findings published. Intermittent infusion of piperacillin/tazobactam 4 g two to four times daily was also associated with underdosage [13,22].

With a total piperacillin clearance of 94 ml/min the clearance is higher than reported in previous studies [18,20-22]. This is due to the larger membrane surface of the polysulfone filter [18,20,26]. This explanation is confirmed by the finding that the calculated volume of distribution of 0.28 l/kg is similar to those already reported [21-23]. Acute renal failure can alter pharmacokinetics of critical ill patients [9]. The prolonged half life and variable values of C_{max} of piperacillin

Patient [No.]	Type of CRRT	AUC24h [mg*h/L]	AUIC [h]
1		CVVHD	n.a.
2	CVVHD	33.29	67
3	CVVHD	107.62	215
5	CVVHD	34.65	69
6**	CVVHD	33.83	68
7	CVVHDF	104.38	209
9	CVVHD	59.63	119
10	CVVHD	54.38	109
11	CVVHD	86.21	172
12	CVVHD	128.52	257
14	CVVHDF	76.87	154
15	CVVHD	52.21	104
16	CVVHD	30.2	60
17	CVVHD	46.63	93
18	CVVHD	63.71	127
19	CVVHD	67.06	134
20	CVVHD	15.45	31
22	CVVHD	69.48	139
23	CVVHD	26.34	59
24	CVVHD	83.23	166
total	-	61.77	124
n.a.: not available			
* AUC values were maximum 20% extrapolated			
** Dose of 400 mg twice daily administered			

Table 2: Effectiveness of ciprofloxacin (200 mg twice daily) calculated for an initial antibiotic treatment (MIC = 0.5 mg/l). Optimum exposure to ciprofloxacin is given when the ratio (AUIC) of AUC and MIC is ≥ 125 h per dosing interval.

are due to several CRRT parameters (CRRT method; dialysate flow; rate of ultrafiltration; blood flow), membrane specific factors (material; surface; coefficient of ultrafiltration) and specifics of patients (organ function; comorbidity, additional drugs). The results are comparable to other studies [18,22-24]. Trotman et al. recommend a piperacillin/tazobactam dosage of 2.25-3.38 g every 6 hours [34]. According to a review of Pea et al. and the study of Arzuaga et al. piperacillin/tazobactam 4.0/0.5 g is to be administered three to four times a day [15,30]. A continuous or prolonged infusion of piperacillin/tazobactam was also tested in clinical trials [32,35-37], but there was no proof of lower mortality rates in a meta analysis [38]. In the study reported here, short-term infusion of piperacillin/tazobactam 4.0/0.5 g resulted in a high interindividual variance. Nearly 50% of the included patients did not match target values during the eight hour dosing interval. In order to avoid underdosing, in a patient population and therapy setting comparable to ours, we recommend increased piperacillin doses. We conclude that in severe sepsis with ARF leading to CRRT when TDM is not available, piperacillin/tazobactam 4.0/0.5g should be administered every six hours.

Ciprofloxacin

The calculated total clearance of 154 ml/min is similar or lower than published study results [19,24,25,27,31]. The mean maximum and minimum serum concentrations were lower than those given in the product information of ciprofloxacin (7.2 mg/l) [39]. A high MIC of bacteria like *Pseudomonas aeruginosa* leading to low AUIC levels are often resulting in therapeutic failures [40]. MIC levels of 0.5 mg/l are in accordance with the EUCAST guideline for a calculated antibiotic therapy [41].

Concentration dependent antibiotics like ciprofloxacin should result in an AUIC > 125 h and a C_{max} /MIC ratio ≥10 in order to guarantee optimum efficacy and tolerability [7,8]. In former studies dosages of 100-400 mg bid were investigated in patients undergoing continuous renal replacement therapy [19,24,26,27]. There is only a case study available reporting the administration of 800 mg ciprofloxacin twice daily in a critically ill patient with multi organ failure [31]. In our study only 9 of 20 patients treated with ciprofloxacin 200 mg twice daily reached the target levels in terms of AUIC and C_{max}/MIC. With 95% probability 29%-76% of patients treated with ciprofloxacin were underdosed and the exposure to ciprofloxacin was too low. A dosage of 400 mg twice daily resulted in a mean AUIC of 161 hours [27] while in the supernatant study a dosage of 200 mg to times a day resulted in an AUIC equal to 124 hours. In accordance with the results of other studies higher doses of ciprofloxacin and TDM is recommended in critically ill patients [34,42]. We conclude that in severe sepsis with ARF leading to CRRT when TDM is not available dosing of ciprofloxacin should be increased to 400 mg twice daily.

Critical illness and the clinical interventions may have various effects on patients'physiology and the pharmacokinetics of drugs. The increase in the volume of distribution in septic patients might result in underdosing. According to the present study results underdosing of piperacillin and ciprofloxacin is most likely. However there is a high inter individual variability. Therefore TDM should be conducted to ensure that antibiotic target concentrations are achieved in the individual patient with respect to the individual state of disease and pathophysiology. Blood sampling and analysis, e.g. simultaneous assaying of different antibiotics as described here, allow direct measurement of antibiotic clearance and calculation of appropriate subsequent dosage in order to achieve target concentrations in the individual patient.

Study Limitations

Concentrations of the antibiotics were measured in plasma which might differ from concentrations at the infection side [43]. CRRT technology got more and more advanced during the last decade. Results and recommendations derived from a specific dialysis procedure cannot be readily transferred to another CRRT setting. Results cannot be extrapolated to other dialysis systems and membranes. Sampling and analysis of the drug concentrations were performed in the steady state phase of antibiotic therapy; results are not representative for the initial phase of treatment. Because early and appropriate dosing of antibiotics is crucial for the outcome loading doses of antibiotics during the first day of treatment are to be considered. The loading dose was not investigated here.

Summary

Despite the moderate rate of Cl_{CRRT}, the exposure of the patients to piperacillin and ciprofloxacin revealed to be inadequate. In critically ill patients undergoing CRRT, piperacillin/tazobactam 4.0/0.5 g should be administered four times a day and ciprofloxacin 400 mg twice daily in order to avoid underdosing. Moreover individualized dosing of antibiotic therapy in terms of therapeutic drug monitoring is worthwhile for critical ill patients undergoing CRRT.

Tweet

In patients undergoing CRRT, piperacillin/tazobactam 4.0/0.5 g should be administered four times a day and ciprofloxacin 400 mg twice daily in order to avoid underdosing.

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