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### **Infectious complications in critically ill patients: focus on clinical, pharmacological and economic aspects**

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## CHAPTER 4

# Pharmacokinetics of cefotaxime during continuous and intermittent infusion in critically ill patients\*

### INTRODUCTION

Parenteral beta-lactam antibiotics such as cefotaxime, a broad-spectrum cephalosporin antibiotic, are widely used in various patients groups including critically ill patients with suspected or proven infections with micro-organisms susceptible to cefotaxime. As is the case in all beta-lactam antibiotics, the microbiological and clinical efficacy is mainly dependent on achieving concentrations well above the minimal inhibitory concentration (MIC) for the causative micro-organism(s) for an adequate period of time, as this class of antibiotics has no clinically relevant post-antibiotic effect. Various studies have demonstrated that bacterial killing is determined by the percentage of time during which antibiotic levels exceed 4-5 x MIC, while bacterial resistance appears to be associated with antibiotic levels below 4-5 x MIC (sub-therapeutic dosing) [1-4].

Recently, we studied the pharmacokinetics and pharmacodynamics of intravenous cefotaxime given either intermittently (1 gram *tid*) or continuously (2 gram daily continuous after a 1 gram loading dose) in moderately ill patients with chronic obstructive pulmonary disease (COPD). We found that a greater proportion of drug levels exceeded MIC and 5xMIC in the continuous group and for a larger proportion of the dosing intervals (time above MIC) [5].

Very few studies have been performed to address the pharmacokinetics of continuous versus intermittent administration of cephalosporins in ICU patients. Various factors may combine in this category of patients that could significantly alter pharmacokinetics, such as impaired renal- and liver function, altered volume of distribution,

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use of numerous co-medications, etc. On the other hand the effectiveness of antibiotic treatment and the prevention of antibiotic resistance may be even more important in the critical care setting than elsewhere, making effective dosing an issue of paramount importance. Therefore, we designed a prospective randomised study to compare the pharmacokinetics of cefotaxime after continuous or intermittent administration in ICU patients.

#### MATERIALS AND METHODS

##### *Study Design*

The study was designed as a randomized controlled prospective open-label study to compare pharmacokinetics of continuous *vs.* intermittent intravenous antibiotic administration. Forty-four consecutive patients meeting our inclusion criteria were enrolled in the study during a 14-month period, and were randomized 1:1 to receive either a continuous infusion of cefotaxime (2 gram continuously per 24h) after an initial loading dose of 1 gram started simultaneously with continuous infusion and given in 30 minutes (group 1, CI), or cefotaxime 1 gram intravenously three times per day (with intervals of exactly 8 hours; group 2, II) infused at a constant rate over a period of 30 minutes.

For intermittent cefotaxime administration we used our conventional strategy of 1 gram *tid* to treat respiratory infections in critically ill patients. The dose for continuous administration was chosen to reach target concentrations of 5 times the MIC for common community acquired bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catharralis*, which are the most frequently cultured causative micro-organisms in respiratory infections in our ICU population in the first days after admission. The MIC's of cefotaxime for these bacteria are below 0.5 mg/l in >99% of our historical cultures. Therefore, to achieve the proper pharmacodynamic effect the historical MIC was multiplied by the desired 5xMIC thereby identifying that a target steady state concentration (C<sub>ss</sub>) of 2.5 mg/l was needed for optimum clinical and bactericidal effect. Continuous infusion dose can be calculated based on the equation: Dose (mg/h) = C<sub>ss</sub> (mg/l) \* Cl (l/h). Based on the known pharmacokinetic data on cefotaxime (half-life (t<sub>1/2</sub>) of 0.9-1.4 hours, total body clearance (Cl) of 15.6-26.4 l/hr, and volume of distribution (V<sub>d</sub>) of 0.3-0.4 l/kg we calculated that a continuous infusion of 2 g cefotaxime over 24 hours would generate steady state concentrations of 3.2-5.3 mg/l. Furthermore, for this group it was calculated that a loading dose of 200 mg would be adequate to achieve concentrations ≥4xMIC for patients weighing 100 kg or less (formula: required dose in mg = concentration at steady state [mg/l] x V<sub>d</sub> [l/kg] x body weight [kg]). However, for practical reasons a loading dose of 1 g was chosen. To be able to compare data with our previous study in less severely ill patients admitted to the general ward

we did not change dosing strategies [5]; the doses were expected to be effective based on the results of this previous study and the known historical microbiological susceptibility data of our ICU patients.

The study was approved by the hospital ethics committee and informed consent was obtained from all participating patients or their legal representatives.

#### *Study Population*

Forty-four consecutive ICU patients (26 male, 18 female) with suspected or confirmed pulmonary infections who met the inclusion criteria for our study were included between January 2003 and February 2004. Requirements for antibiotic therapy were determined by the attending intensivist and a microbiologist based on at least three of the following clinical criteria: fever  $\geq 38.5^{\circ}\text{C}$ , amount of sputum production or change in character/colour of sputum, pathogenic micro-organisms in bronchotracheal aspirate, bronchial lavage- or pleural fluid, leukocytosis, respiratory insufficiency, deterioration of mechanical ventilation parameters and/ or presence of pulmonary infiltrate(s) on the chest radiograph.

Exclusion criteria were infections with suspected or proven micro-organisms resistant to cefotaxime, a history of allergy to beta-lactam antibiotics, neutropenia (absolute neutrophil count  $< 1000$  cells/ $\text{mm}^3$ ), pregnancy, immunosuppressive medications and AIDS. After determining eligibility for study inclusion patients were randomised to receive either continuous infusion (CI) or intermittent infusion of cefotaxime (II).

#### **MICROBIOLOGICAL ANALYSIS**

Although microbiological outcome data were not primary endpoints of our study, we obtained microbiological cultures of sputum, trans-tracheal aspirate, bronchial lavage fluid or pleural fluid whenever possible. Susceptibility to cefotaxime was determined in all samples using routine qualitative susceptibility testing using BD PHOENIX automated microbiology system (Becton Dickinson Diagnostic Systems, Sparks, Md. USA).

#### **PHARMACOKINETIC ANALYSIS**

To determine serum concentrations of cefotaxime, blood samples were drawn at various time points ( $t=1.5$  hours,  $t=3$  hours and  $t=4.5$  hours and  $t=8$  hours after start of intermittent cefotaxime administration during steady state (mean duration after start of treatment after 2 days). For the continuous infusion the start of the loading dose was used as reference time and on day 2, samples were drawn exactly 24, 30 and 36 hours later. Blood samples were collected in tubes without anticoagulant; samples were centrifuged at 1500 rotations/minute for 10 minutes to obtain serum for measuring

cefotaxime concentrations. Samples were frozen and stored at  $-20^{\circ}\text{C}$  until analysis, which was performed within 2 weeks. Serum cefotaxime concentrations were determined using high-pressure liquid chromatography (HPLC). In individual patients maximum concentrations ( $C_{\text{max}}$ ), minimum concentrations ( $C_{\text{min}}$ ) and mean concentrations ( $C_{\text{mean}}$ ) during the 8 h interval were determined.  $C_{\text{mean}}$  is the concentration observed in patients and therefore different from the  $C_{\text{ss}}$  as this is the calculated concentration.

The instruments and materials used were the P2000, AS3000 and SpectraFOCUS HPLC (Thermo Separation Products, San Jose, CA, USA), and a C18-column (Chromspher 5C18/3 mm/10 cm, Varian Analytical Instruments, Bergen op Zoom, The Netherlands). The mobile phase consisted of phosphate buffer (6.8 g/l, pH= 5.5) and methanol in a 92:8 ratio (vol:vol) at a flow rate of 1.3 ml/min. Cefazoline was used as the internal standard. Bovine calf serum (S6648, Sigma Chemical Company, St. Louis, MO, USA) was used to prepare standards and controls as required. Serum protein was removed from each sample by solid phase extraction (SepPak tC18, Waters, Milford, MA, USA). The assay was linear over a range of 0.2 to 125 mg/l. The limit of detection was 0.07 mg/l. Standards of 0.2, 10 and 125 mg/l were used to calibrate the assay (correlation coefficient: 1.000). The mean accuracy and precision (CV%) within-run at the lower limit of quantification (0.2 mg/l) was analysed (n=5) and found to be 96.0% (12.4%). The mean accuracy and precision (CV%) within-run in at 10 mg/l and 125 mg/l were found to be 106.0% (2.3%) and 103.4% (1.87%) respectively. Precision between-runs (repeatability) was analysed (n=10) and found to be 107.8% (2.71%) at 10 mg/l, and 107.0% (4.57%) at 125 mg/l. Recovery was determined by comparing calibration curves in the mobile phase with calibration curves extracted from calf serum. Recovery of cefotaxime was 64.7% (10.2%), and of the internal standard 73.2% (5.5%). Pharmacokinetic calculations of the elimination half-life ( $t_{1/2}$ ), area under the curve extrapolated to infinity ( $\text{AUC}_{0 \rightarrow \infty}$ ), total body clearance (CL) and volume of distribution (at steady state;  $V_{\text{ss}}$ ) were determined by a 2-compartmental pharmacokinetic analysis of serum cefotaxime concentrations for the intermittent administration group versus time data using a commercially available pharmacokinetic software program (MwPharm software version 3.15, (Mediware, Heerenveen, The Netherlands). The model was parameterised in terms of CL and  $V_{\text{d}}$ , after which  $K_{\text{el}}$  was calculated from these values. AUC and  $t_{1/2}$  were calculated from the serum concentrations of cefotaxime. AUC for the continuous administration group is based on calculated mean serum drug concentrations of cefotaxime as measured during continuous infusion, and CL is calculated from the total daily dose and the  $C_{\text{mean}}$  as follows:  $2000/(24 * C_{\text{mean}})$ .

**PHARMACODYNAMIC ANALYSIS**

To address the pharmacodynamics of the population we analysed whether predefined target concentrations of cefotaxime (0.5, 1.0, 2.5 and 5.0 mg/l) could be achieved in both treatment groups. Furthermore, the average time during which antibiotic concentrations were >1 mg/l and >5 mg/l, was calculated in both groups during a representative dosing interval of 8 hours.

**STATISTICAL ANALYSIS**

Results are presented as mean±SD. Students’ t-tests and chi squared tests were used for comparisons between the two study groups. Statistical significance was accepted for P <0.05.

Linear regression was used to evaluate the impact of patient characteristics on the AUC. In order to remove skewness and heteroscedastity, the logtransformed AUC values were used for the analysis. The resulting estimates and confidence intervals were then backtransformed and are presented as percentages. For the multivariate analysis, a forward variable selection method was used. As an additional check on the robustness of the outcome, a backward selection method was carried out with the factors that had a p-value below 0.1 in the univariate analysis.

**RESULTS**

Forty-four patients were included in the study. Characteristics of the included patients are displayed in Table 1. The groups were well matched regarding demographic and relevant clinical variables. Tolerance of cefotaxime in both treatment regimens was excellent, and no specific adverse effects related to the study medication were noted.

Table 1: Patient characteristics			
	intermittent	continuous	P-value
	cefotaxime infusion	cefotaxime infusion	
	n=20	n=24	
Gender (M/F) (%)	13/7 (65%)	13/11 (54%)	P=0.48
Age (years)	69.2±15.8	63.6±20	P=0.31
[range; median]	[21.6-96.9;68.9]	[23.0-88.4;70.2]	
Body Mass Index(kg/m <sup>2</sup> )	24.7±2.2	25.6±4.7	P=0.39
[range; median]	[21.2-30.5;24.6]	[17.7-37.0;24.8]	
Creatinine (µmol/l)	123±86	109±69	P=0.56
[range; median]	[35-431; 97]	[38-274; 85]	
Cockroft Creatinin clearance (ml/min)	66.1±40.3	82.0±49.5	P=0.25
[range; median]	[14.4-170.5;57.7]	[17.5-192.8;71.7]	

Mortality (%)	8/20 (40%)	6/24 (25%)	P=0.31
SOFA-score	6.1±3.3	5.3±3.4	P=0.49
[range; median]	[0-11;6.5]	[0-12;4.5]	
Apache-II score	18.8±6.5	19.3±8.0	P=0.49
[range; median]	[8-37;17.5]	[5-39;18]	
Mechanical ventilation (%)	18/20 (90%)	21/24 (88%)	P=0.80
Duration ICU treatment (days)	8.5±6.2	9.0±8.4	P=0.84
[range; median]	[2-24;6.0]	[2-36;6.0]	

#### MICROBIOLOGICAL EVALUATION

Similar numbers of sputum cultures were collected in both groups: 80% in the intermittent group versus 83% in the continuous group. The percentages of patients with positive sputum cultures did not differ between the groups (65% vs. 63%). A total of 34 pathogens were isolated in 21 patients; 17 pathogens in 10 patients in the intermittent group and 17 pathogens in 13 patients in the continuous group. Cultured pathogens included *Streptococcus pneumoniae* (5), *Hemolytic Streptococcus* (4), *Moraxella catharrhalis* (3), *Escherichia coli* (2) and *Haemophilus influenzae* (2). We immediately switched antibiotics if pathogens not susceptible to cefotaxime were cultured. However, the pharmacokinetic data from these patients were still used if all measurements during cefotaxime infusion had been obtained.

#### PHARMACOKINETIC EVALUATION

Cefotaxime serum concentrations were measured in 44 patients based on a total of 158 samples. Pharmacokinetic outcome parameters are shown in table 2 and figures 1-3.

Table 2: Pharmacokinetic evaluation of continuous cefotaxime (2g/24 hours) versus intermittent cefotaxime administration (1 g tid/ 8 hours) in ICU patients.			
	intermittent	continuous	P-value
	cefotaxime infusion	cefotaxime infusion	
	n=20	n=24	
Evaluable patients (n)	20	24	
C <sub>max</sub> (mg/l)	68.2±14.4	12.1±7.7	P<0.01
[range;median]	[42.2-94.4;66.3]	[2.3-0.4;10.8]	
C <sub>mean</sub> (mg/l)	24.3±18.9	10.7±7.4	P<0.01
[range;median]	[4.5-82.1;19.0]	[2.2-40.1;10.1]	
C <sub>min</sub> (mg/l)	4.6±7	9.5±7.3	P=0.03
[range;median]	[0-30;2.3]	[2.1-39.4;8.7]	
AUC (mg*h*24/l)	584.1±453.4	257.8±176.7	P<0.01
[range;median]	[107.3-1971.4;457.2]	[53.4-961.6;242.4]	

Vss (l)	25.5±16.5	NA*	
[range;median]	[10.3-68.2;19.6]	NA	
T <sub>1/2</sub> α (h)	0.5±0.1	NA*	
[range;median]	[0.4-0.7;0.6]	NA	
T <sub>1/2</sub> β (h)	3.7±3.0	NA*	
[range;median]	[1.1-12.3;2.6]	NA	
Cl (l/h)	6.5±5.6	11.1±7.9	P=0.03
[range;median]	[1.6-28.1; 5.8]	[2.1-37.5; 8.3]	

\* Vd and T<sub>1/2</sub> not calculated during continuous infusion

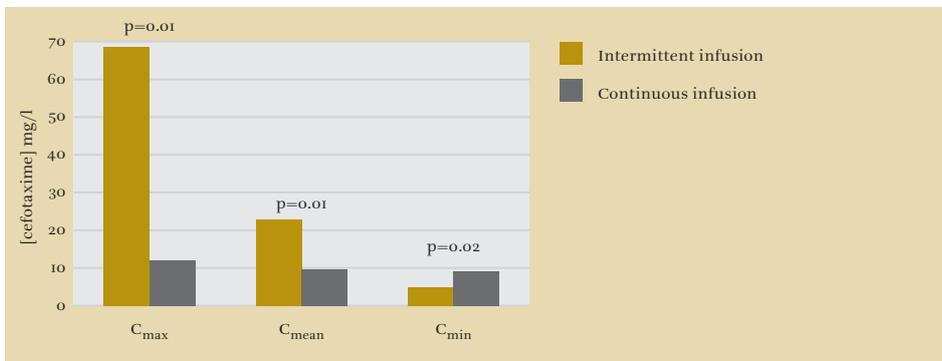


Figure 1: Maximum, mean and minimal cefotaxime concentrations in the intermittent infusion group (1 g tid 8h ;3g/24 h) vs. continuous infusion (2 g /24 h)

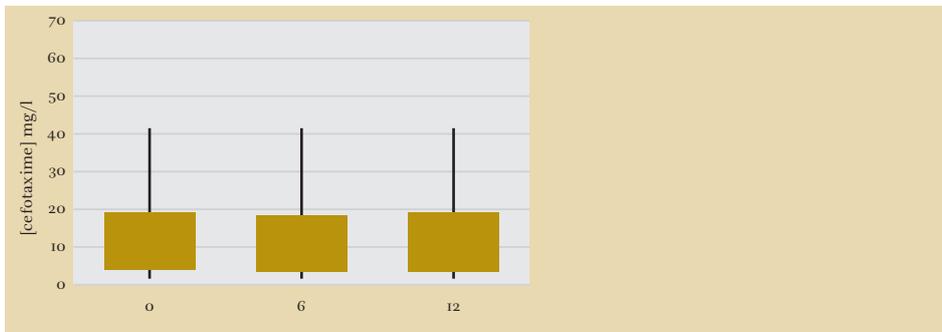


Figure 2: Cefotaxime serum level variations in continuous infusion group during 12 hour dosing interval of 1 g per 12 hours (Boxes represent mean ± SD and lines minimum-maximum ranges)

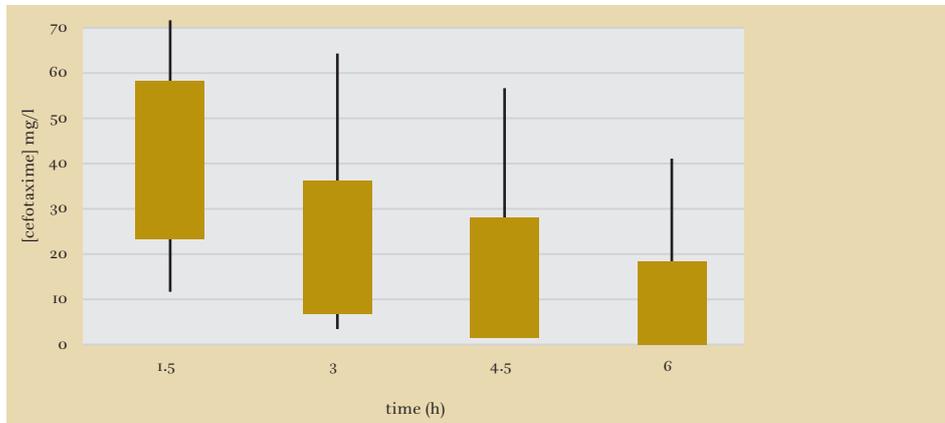


Figure 3: Cefotaxime serum level variations in intermittent infusion group during 8 hour dosing interval (Boxes represent mean  $\pm$  SD and lines minimum-maximum ranges)

In patients treated with continuous cefotaxime infusion the mean total serum drug concentration ( $C_{\text{mean}}$ ) was  $10.7 \pm 7.4$  mg/l [range 2.2-40]. This concentration was significantly lower than the  $C_{\text{mean}}$  in the intermittent group, which was  $24.3 \pm 18.9$  mg/l [range 4.5-82.1] ( $P < 0.01$ ). This is partly explained by the higher dose given to the intermittent group. AUC was 114% higher in the intermittent group than observed in the continuous group, while daily dosages used were only 50% higher (3g vs. 2 g). After correction for treatment effect AUC correlated significantly with age ( $P = 0.01$ ) and creatinine ( $P = 0.003$ ). After application of multivariate analysis AUC was only significantly influenced by infusion strategy; 100% (40%-189%;  $P = 0.0003$ ) higher in the intermittent group and creatinine doubling; 43% (14%-80%;  $P = 0.003$ ). This means that after correction for creatinine AUC was 100% higher in the intermittent group and if the creatinine levels of a single patient are twice as high compared to another patient AUC is expected to be 43% higher.

In the intermittent group the average peak antibiotic concentration ( $C_{\text{max}}$ , measured at  $t = 0.5$  hours) was  $68.2 \pm 14.4$  mg/l, while mean trough concentration ( $C_{\text{min}}$ ; measured just before administration of a new dose) was  $4.6 \pm 7$  mg/l [range 0-30]. Although  $C_{\text{max}}$ ,  $C_{\text{mean}}$  and AUC were significantly higher in the intermittent group with P-values  $< 0.01$ ,  $C_{\text{min}}$  was significantly lower ( $P < 0.01$ ). Large variations in cefotaxime concentrations in individual patient were observed in both groups. Mean total drug clearance (Cl) was statistically different between the two groups ( $6.5 \pm 5.6$  (II) vs.  $11.1 \pm 7.9$  l/h (CI);  $P = 0.03$ ).

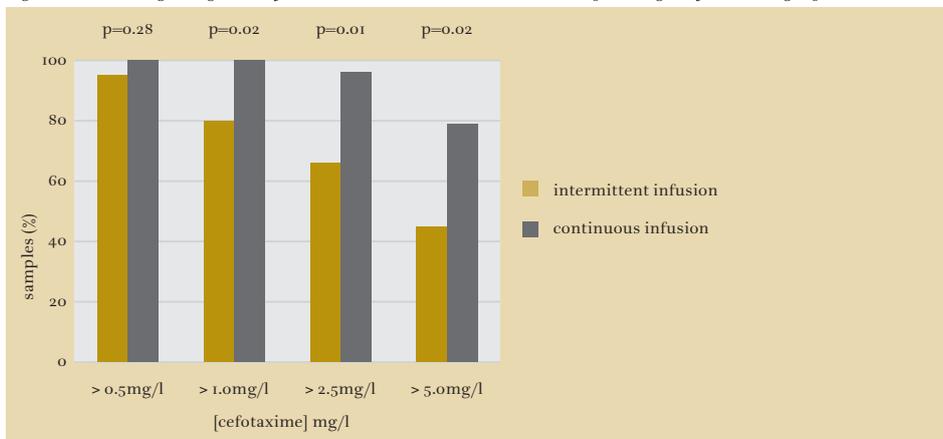
#### PHARMACODYNAMIC EVALUATION

Cefotaxime concentrations  $> 2.5$  mg/l were measured in 96% of all samples in the continuous group versus 65% in the intermittent group ( $P = 0.01$ ). Drug concentrations  $> 5$  mg/l were noted in 79% of all samples in the continuous group vs. 45% in the intermittent

group ( $P=0.02$ ) (table 3, figure 4). The percentage of time during an 8 hour dosing interval during which cefotaxime concentrations exceeded 1,0 mg/l and 5,0 mg/l, respectively, were similar in the two groups, and sufficiently exceeded the commonly used thresholds for effective therapy of 60-70% of time above 4-5x MIC (table 3, figure 5).

Table 3: Single sample analysis and percentage of time above cut-off cefotaxime concentrations			
	intermittent	continuous	P-value
	cefotaxime infusion	cefotaxime infusion	
	n=20	n=24	
Evaluable patients (n)	20	24	
single cefotaxime levels > 5.0 mg/l (n/%)	9/20 (45)	19/24 (79)	$P=0.02$
single cefotaxime levels > 2.5 mg/l (n/%)	13/20 (65)	23/24 (96)	$P=0.01$
single cefotaxime levels > 1.0 mg/l (n/%)	16/20 (80)	24/24 (100)	$P=0.02$
single cefotaxime levels > 0.5 mg/l (n/%)	19/20 (95)	24/24 (100)	$P=0.28$
percentage time > 1.0 mg/l (mean±sd)	95.1±10.9	100±0	$P<0.01$
percentage time > 5.0 mg/l (mean±sd)	77.6±23.9	95.1±10.9	$P=0.13$

Figure 4: Percentage single samples in continuous and intermittent infusion group exceeding cefotaxime



concentration defined cut-off points

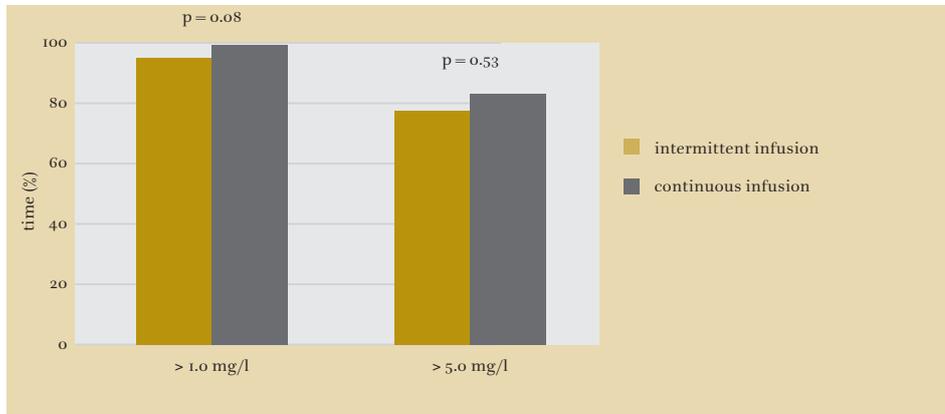


Figure 5: Percentage of time that cefotaxime concentrations exceed defined cut-off values during 8 hours dosing interval

#### DISCUSSION

The results of our study demonstrate that, in terms of pharmacokinetics, continuous administration of cefotaxime leads to longer time periods with effective serum drug concentrations in ICU patients with respiratory infections than intermittent administration.

Antibiotic concentrations  $>4-5\times$  MIC for at least 60-70% of treatment time are thought to be required for microbiological efficacy, and to avoid induction of antibiotic resistance [1-4]. A clear trend was observed in the duration that drug levels exceeded predefined optimum drug concentration targets (MICs) in favour of the continuous administration group, although this difference failed to reach statistical significance in this relatively small group of patients. These differences were observed in spite of the fact that overall dosage was 1 gram per day lower in the continuous group.

Although intermittent dosing also provided sufficient coverage in most patients, significantly more measurements with drug levels below optimum serum drug concentration targets (MICs) were found in the intermittent group. Therefore, a better pharmacodynamic profile could be achieved with continuous infusion, especially near the end of each dosing interval, although  $C_{max}$ ,  $C_{mean}$  and AUC were lower in this group. The difference in  $C_{max}$ ,  $C_{mean}$  and AUC is partly caused by a difference in the total daily dose (2 g CI vs. 3 g II) however 100% higher AUC in the intermittent group cannot only be explained by a 50% higher daily dose. Possibly diminished clearance in the intermittent dosing regimen is due to saturable elimination mechanisms caused by higher  $C_{max}$ ,  $C_{mean}$  and AUC in this group. The observed effect was independent of renal function.

Based on the pharmacodynamics of cefotaxime the time above MIC is more important than  $C_{max}$ ,  $C_{mean}$  and AUC. The higher  $C_{max}$ ,  $C_{mean}$  and AUC in the intermittent administration group should not lead to the assumption that these parameters are superior to the lower values observed during continuous infusion. Like all other antibiotics in the class of beta-lactam antibiotics, cefotaxime, has no clinically relevant post-antibiotic effect and therefore the risk of suboptimal treatment will be near the end of the dosing interval. With respect to the  $C_{min}$  a better performance during continuous infusion could be demonstrated.

Recently, we performed a similar study in less severely ill patients with COPD and respiratory infections who were admitted to the general ward. In these patients we observed that continuous infusion and intermittent administration of cefotaxime were equally effective with respect to pharmacokinetics and clinical endpoints [5]. However, the pharmacodynamic profile in the continuous infusion group was superior to the intermittent administration group.

With respect to pharmacokinetics we observed higher mean drug levels of cefotaxime in ICU patients compared to COPD patients, both in the intermittent group ( $24.3 \pm 18.9$  mg/l vs.  $8.6 \pm 3.3$  mg/l) and in the continuous infusion group ( $10.7 \pm 7.4$  mg/l vs.  $5.6 \pm 1.9$  mg/l).

Renal dysfunction may affect antibiotic concentrations in the critically ill patient, as has been demonstrated previously [6]. An important route of elimination for cephalosporins is renal clearance. Therefore, the higher drug levels in ICU patients may be due to the more profound disturbances in renal function *i.e.* lower creatinine clearance in the ICU population compared to the COPD group (Cockcroft-Gould creatinine clearance in the intermittent group:  $66.1 \pm 40.3$  ml/min (ICU) vs.  $80.7 \pm 23.8$  ml/min (COPD) and in the continuous group  $82.0 \pm 49.5$  ml/min (ICU) vs.  $85.5 \pm 25.2$  ml/min (COPD). Furthermore, in the intermittent ICU administration group compared to the continuous administration group higher drug levels were encountered, than could be expected for based on the difference in daily dose of cefotaxime. There was a significantly lower drug clearance in this group ( $6.5 \pm 5.6$  l/h vs.  $11.2 \pm 7.9$ ;  $P=0.03$ ). This difference is only partly caused by a lower creatinine clearance in the intermittent group (11% of the effect), as after correction for renal function still a 100% higher AUC is observed in the intermittent group with a 50% higher daily dose; no such difference was observed in our earlier study in less severely ill patients. This observation emphasizes the importance of renal function on cefotaxime drug clearance. In contrast to our expectations, volumes of distribution in the ICU population were similar to those observed in our earlier study ( $25.5 \pm 16.5$  l (current study) vs.  $22.6 \pm 3.9$  l (previous study)).

We observed huge variabilities in mean drug levels between patients in both groups, with up to 18-fold differences (figures 2 and 3). These differences are much greater than those observed in our previous study in less severely ill patients, where up to 5-fold differences were observed. This suggests that a fixed dose strategy may lead to high drug levels in some patients, and to low or even insufficient drug levels in others. There are several ways to circumvent this problem. First, a higher fixed dose may reduce the risk of suboptimal drug levels; however, this could increase the risk for dose-related toxicity and more use of antibiotics has been related to the emergence of resistance. Continuous infusion may add to the efficacy for reasons of pharmacodynamic superiority in the drug levels at the end of the dosing interval. From a theoretical perspective this could be a better solution than to simply increase the doses.

Alternatively, therapeutic drug monitoring (TDM) could be used to measure drug levels achieved in individual patients. During continuous infusion it is feasible to predict minimum concentrations (which is a relevant parameter for antibiotics expressing no or marginal post-antibiotic effect) based on 1 or 2 serum drug samples. In intermittent dosing TDM may be more complex, costly and time consuming.

Another potential advantage of continuous administration was demonstrated in a previous study, addressing workload and costs of intravenous antibiotics administration [7]. This study demonstrated that when all cost drivers are taken into account, the cheapest method of administering intravenous antibiotics was through use of a continuous syringe pump. The differences between administration methods were largely due to differences in time expenditure by relatively highly trained (and paid) certified nurses or physicians. Moreover, intermittent dosing often requires slow infusion of the antibiotic, which also implies a greater expenditure of time [7].

Our study has some limitations. Our study was designed to assess pharmacokinetic and pharmacodynamic parameters and was underpowered to detect differences in clinical outcome and mortality as well as microbiological cure rates.

Translation of the results regarding pharmacodynamic superiority of continuous antibiotic administration to potential clinical superiority should therefore be viewed with great caution. However, in our previous study in COPD patients we were able to demonstrate that at the very least there were no disadvantages of continuous infusion with respect to clinical and microbiological cure rates and development of resistance. Therefore, it seems likely that similar results would be achievable in critically ill patients. This view is supported by the results of some other studies. Nicolau *et al.* demonstrated equipotence in clinical outcome, microbiological cure rates and emergence of antibiotic resistance when comparing different methods of administration of ceftazidime, another cephalosporin beta-lactam antibiotic, in critically ill patients [8].

Other studies assessing continuous administration of cephalosporins (mostly ceftazidime) in critically ill patients also found equivalent drug levels compared to bolus administration [9-13]. However, without exception more optimal drug levels were encountered near the end of the dosing intervals in these studies, suggesting a more favourable pharmacodynamic profile for antibiotics whose killing capacity depends on time >MIC.

In conclusion, we observed that continuous infusion of cefotaxime in critically ill patients leads to equal or better pharmacodynamic profiles compared to intermittent cefotaxime administration. These results were achieved using a lower daily dose during continuous infusion. In both groups the drug levels exceeded threshold drug targets (MIC) for more than 60-70% of each dosing interval. Potentially costs and workload could be reduced by using continuous rather than intermittent dosing. The large inter-patient variability observed in both study groups underlines the potential risk of suboptimal dosing in individual patients. This problem could be circumvented by TDM, which on theoretical grounds would be easier in case of continuous administration. In addition, the time intervals during which drug levels drop below MIC thresholds appeared to be lower when continuous administration was used. Based on these advantages we recommend continuous rather than intermittent administration of cefotaxime as the preferred method in critically ill patients.

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