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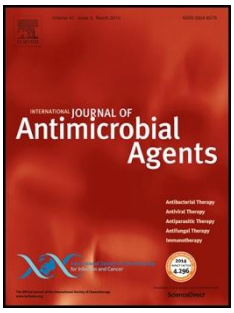

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Target attainment with continuous dosing of piperacillin/tazobactam in critical illness: a prospective observational study

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Highlights

- Continuous dosing of piperacillin in critical illness does not yield a high sustained target.
- Large variability in concentrations is seen in continuous dosing of piperacillin.
- Higher continuous dosing of piperacillin and therapeutic drug monitoring is needed.

ABSTRACT

Optimal dosing of β-lactam antibiotics in critically ill patients is a challenge given the unpredictable pharmacokinetic profile of this patient population. Several studies have shown intermittent dosing to often yield inadequate drug concentrations. Continuous dosing is an attractive alternative from a pharmacodynamic point of view. This study evaluated whether, during continuous dosing, piperacillin concentrations reached and maintained a pre-defined target in critically ill patients. Adult patients treated with piperacillin by continuous dosing in the intensive care unit of a university medical centre in The Netherlands were prospectively studied. Total and unbound piperacillin concentrations drawn at fixed time points throughout the entire treatment course were determined by liquid chromatography–tandem mass spectrometry. A pharmacokinetic combined target of a piperacillin concentration ≥80 mg/L, reached within 1 h of starting study treatment AND maintained throughout the treatment course, was set. Eighteen patients were analysed. The median duration of monitored piperacillin treatment was 60 h (interquartile range, 33–96 h). Of the 18 patients, 5 (27.8 %) reached the combined target; 15 (83.3%) reached and maintained a less strict target of >16 mg/L. In this patient cohort, this dosing schedule was insufficient to reach the pre-defined target.

Depending on which target is to be met, a larger initial cumulative dose is desirable, combined with therapeutic drug monitoring.

1. Introduction

Infections, both community-acquired and nosocomial, are a constant source of morbidity and mortality in critically ill patients [1]. β-Lactams, with or without a β-lactamase inhibitor, are the most prescribed group of antibiotics in this setting [2,3]. Guidelines for the management of severe sepsis and septic shock advocate the initiation of antibiotics as soon as possible, using broad-spectrum antibiotics that penetrate in adequate concentrations at the presumed site of infection, ensuring optimal activity against all likely pathogens [4]. Choosing appropriate therapy is crucial, as inadequate antimicrobial treatment is an important determinant of poor outcome [5]. Optimal dosing is equally important because inadequate dosing leads to treatment failure and antibiotic resistance [6].

Piperacillin/tazobactam (TZP) is a widely used β-lactam/β-lactamase inhibitor combination. The effectiveness of piperacillin is determined by the time the unbound plasma concentration (*f*T) is higher than the minimum inhibitory concentration (MIC) of the causative bacteria ($fT_{>MIC}$) [7]. A maximum kill rate is achieved at a free drug concentration of ca. 4× MIC [8], with no additional effect above this concentration. There is no relevant post-antibiotic effect against Gram-negative micro-organisms [9]. Dosing regimens have traditionally been based upon pharmacokinetics as tested in vitro, in animal models and in healthy volunteers [6,10–12]. However, in critical illness, several complex mechanisms induce an altered pharmacokinetic profile owing to, for example, an increase in volume of distribution and an alteration in renal clearance [11]. Numerous studies have shown inadequate drug concentrations in critically ill patients treated with

β-lactams using conventional dosing regimens [13–20]. In particular, augmented renal clearance, as might occur during the hyperdynamic stage of sepsis, appears to be a risk factor for failing to reach adequate β-lactam drug levels [15–19].

From a pharmacodynamic point of view, continuous infusion is an attractive alternative to conventional intermittent dosing of β-lactams. This is also supported by clinical studies [21–25], The critical care population is likely to gain the most benefit from continuous dosing as this group tends to harbour pathogens with higher MICs [26] and to have an unpredictable pharmacokinetic profile [11]. Although high-quality randomised trials showing a survival benefit are still lacking, in a recent meta-analysis of individual patient data from three randomised trials, treatment with β-lactam antibiotics by continuous infusion was associated with lower mortality compared with intermittent dosing in critically ill patients with severe sepsis [24]. Continuous dosing of TZP, however, is not yet widely employed in European intensive care units (ICUs) [27].

This prospective study was conducted to evaluate whether, during continuous dosing, piperacillin concentrations reach and maintain a high target concentration in critically ill patients, likely to cover most problematic pathogens such as *Pseudomonas aeruginosa.*

2. Materials and methods

2.1. Study design and study population

This prospective, observational, single-centre, cohort study was conducted in the Department of Critical Care of University Medical Center Groningen (UMCG) (Groningen, The Netherlands) between December 2013 and January 2015. The study was approved by the Medical Ethics Board of this hospital. Written informed consent was obtained from the patient or their next of kin. Patients were eligible for inclusion at the start of treatment with TZP for suspected or proven infection. Start of treatment was at the discretion of the treating physician. Inclusion criteria were: indication for treatment with TZP; admitted to the ICU; age ≥18 years; and able to give informed consent or legal representative able to give informed consent. All patients had an indwelling arterial line for reasons outside the study protocol. Exclusion criteria were: pregnancy; severe anaemia; use of renal replacement therapy; and contra-indications to continuous infusion. Patients already started on TZP by intermittent dosing (e.g. on the ward, before ICU admission) were included if no more five doses had been given; continuous dosing was started directly after a next bolus.

All patients, regardless of kidney function, received a loading dose of 4 g/0.5 g TZP (Piperacillin/Tazobactam Fresenius Kabi 4g/0.5g powder for solution for infusion; LABESFAL Fresenius Kabi Group, Santiago de Besteiros, Portugal) infused over 20 min. Continuous dosing was started directly after the loading dose in all patients using a syringe pump (Alaris® GH perfusor; CareFusion, Rolle, Switzerland). The first hour of starting treatment, including infusion of the loading dose over 20 min directly followed by

continuous infusion, was considered the loading phase. The next phase, from 1 h after the start of treatment, was referred to as the maintenance phase. The sample drawn at 1 h after the start of treatment was considered as part of the maintenance phase. The dosing schedule for continuous infusion in the maintenance phase was adjusted to renal function [assessed by calculation of creatinine clearance (CL_{Cr}) over 24-h intervals using the equation: Urine creatinine (mmol/L) × Urine volume (mL)/time (min) × Serum creatinine (mmol/L) (UCreat × UVol/time × SCreat); or, when parameters not were available, estimated using the Modification of Diet in Renal Disease (MDRD) formula for estimated glomerular filtration rate]. Renal function was recorded on the day of starting treatment with TZP in the context of the study.

Patients with a CL_{Cr} > 40 mL/min received a continuous infusion of 12/1.5 g TZP every 24 h. Patients with a CL_{Cr} of 20–40 mL/min received a continuous dose of 8/1 g on Day 1 and 12/1.5 g from Day 2 onwards. Patients with a CL_{Cr} < 20 mL/min received a continuous dose of 8/1 g from Day 1. Blood samples were drawn at the start of treatment in the context of the study on Day 1 and then at 20 min after the start of treatment (directly after the loading dose); subsequent samples were drawn at 40 min and at 1, 2, 4, 8, 12 and 24 h after the start of treatment; from Day 2, samples were drawn every 12 h for a maximum period of 2 weeks or until treatment with TZP was stopped. Samples were centrifuged and were frozen at –20 °C, to be processed in batch by the Department of Clinical Pharmacy and Pharmacology of UMCG. Patient characteristics included demographic and clinical data, assessment of illness severity

reflected by the Acute Physiology and Chronic Health Evaluation (APACHE) IV score, and laboratory investigations.

2.2. Definition of pharmacokinetic/pharmacodynamic (PK/PD) target

A 'strict' target was chosen based on the notion that for β-lactams, a maximum kill rate is achieved at a free (unbound) drug concentration of ca. 4× the MIC of a causative organism, with no additional effect above this concentration [8,28] and the absence of a relevant post-antibiotic effect against Gram-negative organisms [9]. *Pseudomonas aeruginosa* was chosen as a possible causative micro-organism in consideration of a 'worst-case scenario', with an MIC clinical breakpoint of 16 mg/L (http://www.eucast.org/clinical_breakpoints/; accessed 21 May 2016), to cover most problematic pathogens [29] in an empirical treatment setting.

The pre-defined PK/PD target was thus set at 100%$T_{\geq 5xMIC}$ (percentage of time of dosing interval during which the total concentration exceeds 5× MIC), assuming 20–30% protein binding [30,31], implying a target of 4 × 16 = 64 mg/L for unbound and 5 × 16 = 80 mg/L for total piperacillin concentration. This target is in line with targets set by other research groups considered experts in the field [14,32] as well as reviews addressing the pharmacokinetics of β-lactams [8,33,34]. This target was to be met from 1 h after the start of treatment in the context of the study, i.e. during the maintenance phase; 1 h after start of the last bolus infusion directly followed by continuous infusion, and to be maintained thereafter; we will refer to this as a combined target (target reached within 1 h AND maintained thereafter). Reaching a target of >16 mg/L

piperacillin in the maintenance phase, i.e. at 1 h after the start of treatment and maintained thereafter, 100%$T_{>1xMIC}$, was also determined. For unbound concentrations, a target of ≥4× MIC (64 mg/L) was set. Target attainment was evaluated at sample level as well as in individual patients. Whether the target concentration was reached at 1 h after start of treatment in the context of the study was also assessed.

2.3. Bioanalysis of piperacillin serum concentrations

Total serum concentrations of piperacillin were determined at the Laboratory for Clinical Toxicology and Drugs Analysis of the Department of Clinical Pharmacy and Pharmacology of the UMCG using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay. In brief, all analyses were performed on a triple quadrupole LC-MS/MS system (Thermo Scientific, San Jose, CA) with a Finnigan™ Surveyor® LC pump and a Finnigan™ Surveyor® autosampler (Thermo Scientific). The mobile phase consisted of an aqueous buffer (containing ammonium acetate 5 g/L, acetic acid 35 mL/L and trifluoroacetic acid 2 mL/L water), water and acetonitrile. For chromatography, an Atlantis® HILIC Silica analytical column (2.1 × 100 mm, 3 μm) (Waters, Etten-Leur, The Netherlands) was used. A simple procedure for protein precipitation was used to prepare the samples. For piperacillin, the transition m/z 518.0 to 114.8 (collision energy 51 eV) was measured with a scan width of 0.5 m/z. The calibration curve ranged from 0.5–80 mg/L for piperacillin with a correlation coefficient of 0.99941. Within-run coefficient of variation (CV) ranged from 2.5–12.9% and between-run CV ranged from 5.9–12.5%. Bias ranged from –13.4% at the lower limit of quantification (LLOQ) level to 10.1% at high level. Unbound piperacillin concentrations

were determined in all patients at 1 h and 12 h after the start of treatment. Samples were prepared by ultrafiltration of the corresponding serum samples; 10 μL of human serum was directly transferred into the upper reservoir of the centrifuge filters (Nanosep® 30 K Omega centrifugal device; Pall Corp.) and 200 μL of the internal standard solution was added. The centrifuge filters were closed and the samples were briefly homogenised using a vortex mixer. Filtration was done by centrifugation for 10 min at 12 000 × *g*.

2.4. Statistical analysis

Target attainment was presented as a percentage; percentage of time at or above target per subject and percentage reaching target at group level. Continuous parameters were depicted in absolute numbers and either mean ± standard deviation (S.D.) or median [interquartile range (IQR)], depending on the distribution. Categorical data were depicted as percentage per/in category. Outliers in concentration data were investigated per patient in the maintenance phase (i.e. from 1 h after the start of treatment and onwards) and were defined as values outside the range of 3 × IQR + Q3 to Q1 – 3 × IQR; these were subsequently excluded from the variability analysis and were assessed for exclusion in the target attainment analysis. In the boxplot, they were investigated per sampling period. To quantify within-patient variability, a CV per patient was calculated, defined as a patient's individual S.D. divided by the mean of this patient's concentrations, as measured during the maintenance phase, multiplied by 100%. The median, mean and range of these individual CVs were calculated. To quantify between-patient variability, we chose to calculate a CV for available

concentrations measured at 40 min and at 12, 24, 48 and 60 h after the start of treatment in all patients, respectively. A median, mean and range of these five CVs were calculated. Statistical analyses were performed using SPSS Statistics for Windows v.22 (IBM Corp., Armonk, NY).

3. Results

3.1. Patient characteristics

Twenty patients were included in the study; two patients were excluded because of breach of protocol. Baseline characteristics and clinical outcome data of this typical ICU population are presented in Table 1. Almost all patients required vasopressors and mechanical ventilation (94.4% and 88.9%, respectively). The median length of ICU stay was 9 days (IQR, 3–13.3 days). Four patients (22.2%) died in the ICU; none of the other patients died in hospital. Causes of death in the four patients were decompensated liver cirrhosis with subsequent multi-organ failure, severe traumatic brain injury, massive intrathoracic bleeding after oesophageal resection complicated by anastomotic leakage, and sepsis following chronic osteomyelitis.

3.2. Piperacillin concentration data

In the 18 patients, 53 samples taken during the loading phase and 175 samples taken during the maintenance phase were available for analysis. The median follow-up (duration of piperacillin treatment including sampling of piperacillin concentrations) was 60 h (IQR, 33–96 h). Three outliers were excluded from the analysis. Two outliers were

included as they represented very high values at the beginning of the sampling period most likely due to interindividual variability or to procedural reasons.

Of 172 samples in the maintenance phase, 73 (42.4 %) were at or above the pre-defined target concentration of 80 mg/L; 168 (97.7%) were >16 mg/L. In 16 (88.9%) of 18 patients a concentration of ≥80 mg/L was reached within 1 h after the start of treatment. However, in only 5 (27.8%) of 18 analysed patients was a concentration of ≥80 mg/L maintained (i.e. reached the combined target). Two patients (11.1%) never reached a concentration ≥80 mg/L. On patient level, a median of 39.6% of samples per patient in the maintenance phase were ≥80 mg/L (IQR, 15.5–100.0 mg/L).

All patients had a concentration >16 mg/L within 1 h after the start of treatment. In 15 patients (83.3%), a concentration >16 mg/L was maintained. The data are summarised in Table 2 and Fig. 1.

Two of the four deceased patients had piperacillin levels ≥80 mg/L at any time during treatment, from 1 h after the start of treatment.

All of the patients with a CL_{Cr} < 50 mL/min (7 patients) reached a piperacillin concentration ≥80 mg/L within 1 h of starting treatment, and 3 (42.9%) of the 7 maintained a concentration ≥80 mg/L. In patients with a CL_{Cr} ≥ 50 mL/min (11 patients), 9 (81.8%) reached a piperacillin concentration ≥80 mg/L within 1 h of starting treatment and 2 (18.2%) of 11 maintained a concentration ≥80 mg/L. Measurement of CL_{Cr} by

UCreat × UVol/time × SCreat was available in 13 of 18 patients; in 5 patients renal function was estimated using the MDRD formula.

Unbound piperacillin concentrations assessed at 1 h after the start of treatment (total, 18 samples in 18 patients) were ≥64 mg/L (4× MIC) in 16 (88.9%) of 18 samples and were >16 mg/L in all 18 samples (100%). Unbound piperacillin concentrations assessed at 12 h after the start of treatment (total, 18 samples in 18 patients) were ≥64 mg/L in 7 (38.9%) of 18 samples and were >16 mg/L in all 18 samples (100%). The median fraction unbound was 0.93 [IQR, 0.89–0.97].

3.3. Variability

The median within-patient CV was 32.3% (mean, 39.7%), with a range of 10.3–99.2%.

Concentrations analysed at 40 min and at 12, 24, 48 and 60 h after the start of treatment for between-patient variability were available for 18, 18, 15, 10 and 10 patients, respectively. Median CV for the five time points was 71.8% (mean, 78.7%), with a range of 55.4–99.9%.

Five outliers were excluded from the calculation of the within-patient and between-patient CV.

4. Discussion

To the best of our knowledge, this is the first observational study describing piperacillin concentrations over the entire treatment period in a heterogeneous group of adult ICU patients treated with continuous dosing. As expected, most patients showed a rapid rise in piperacillin concentration after receiving a loading dose; indeed, the vast majority (88.9%) reached the pre-defined target concentration of ≥80 mg/L within 1 h after the start of treatment. Over the course of time, however, despite continuous administration, a large inter-individual and intra-individual variability in piperacillin concentrations was observed in this population, with a trend toward lower concentrations over time (Fig. 1). This large variability was also found in a recent study evaluating extended, i.e. prolonged but not continuous, infusion of piperacillin in ICU patients [35].

Overall, the combined target of a total piperacillin concentration ≥80 mg/L reached within 1 h after starting study treatment AND maintained throughout the treatment course was met in only 27.8% of patients. Large recent studies analysing conventional dosing of β-lactams showed similar results, where pre-defined targets were not met in a large proportion of patients [13,15].

Total and unbound piperacillin concentrations were compared in a subset of samples; as expected, the difference between free and total concentrations was small. Because this difference is small, the cheaper and easier total concentration will suffice, as employed by others [36].

Toxic levels of piperacillin are not well defined in the literature. No clinical signs of overdosing (convulsions) were seen in the current cohort.

Although a matter of debate, we chose an 'aggressive' combined target of 100%$T_{\geq 5xMIC}$ for total piperacillin concentration in the maintenance phase, with a presumed protein binding of ca. 20–30% for piperacillin, using the piperacillin MIC breakpoint for *P. aeruginosa*. Within the set definition, the target concentration was to be met within a small timeframe, i.e. 1 h. PK/PD indices vary widely in the literature, ranging from 100%$fT_{>MIC}$ to 40–100%$fT_{>4xMIC}$ for unbound piperacillin concentrations [37]. There is no conclusive evidence as to which target is required for an optimal therapeutic effect. Altered pharmacokinetics in the critical care patient and possible infection by pathogens with an MIC at or near the resistant breakpoint increase the risk of underdosing [11]. We chose the strict combined target to ensure maximum killing of most problematic (Gram-negative) pathogens in a primarily empirical treatment setting. Supplementary Table S1 illustrates the consequence of different target levels. Obviously, target attainment is influenced by the MIC judged to be relevant as dictated by local resistance patterns. A less strict target of 100%$T_{>MIC}$ was still not met in 16.7% of patients (Table 2). Assuming the great majority of Gram-negatives to have an MIC < 16 mg/L would allow to start using the 'one size fits all' continuous dosing schedule, as was done in this study. Sampling for therapeutic drug monitoring (TDM) could then be done at any time during the maintenance phase to enable proper dose adjustment; in combination with culture results, assuming that these are available, this could mean lowering the dosing schedule in a substantial proportion of the population. However, if more resistant

pathogens are cultured or if expected higher targets have to be met, the perspective changes. This would then make a case for TDM throughout the course of treatment. Piperacillin has a large therapeutic range. In this study, lower piperacillin concentrations were found over the course of treatment and a suboptimal target was attained, even when a lower target of 100%$T_{>MIC}$ was set. Therefore, it seems safe and logical to start a larger cumulative dosing regimen, e.g. 16 g daily of piperacillin infused over 24 h, preceded by a loading dose of 4 g of piperacillin infused over 20 min, in a 'hit fast, hit high' strategy, followed, if possible, by downgrading based on TDM and cultured causative micro-organism.

In our view, strengths of this study include it being the first observational study describing piperacillin concentrations in adult ICU patients treated with continuous dosing over the entire treatment period. Furthermore, total as well as unbound concentrations were assessed.

This study also has some limitations. Only piperacillin concentrations were analysed, not tazobactam. Piperacillin and tazobactam pharmacokinetics are not identical and in patients with renal function loss tazobactam overdose might occur [38]. As outlined in the methods, in several patients piperacillin treatment was started intermittently before start of the study. As treatment was given in intervals of 8 h, in these patients it was still relevant to assess whether the target was met after the start of study treatment, i.e. continuous dosing directly after a bolus infused over 20 min.

Some samples were excluded from analysis as they were identified as outliers. Measurement of CL_{Cr} by UCreat × UVol/time × SCreat was not available in all patients; in 5 of 18 patients renal function was estimated using the MDRD formula. In this analysis, renal function measured/estimated on the first study day was used. In daily practice, however, in most patients CL_{Cr} was measured and in no alteration in dosing due to significant changes in CL_{Cr} was needed. Patients with renal replacement therapy or other extracorporeal support were excluded because in these patients we considered kinetics to be so complicated that this deserves a separate study. The sample size was too small to identify subgroups that would benefit most from TDM.

5. Conclusions

These data show a large variability in piperacillin concentrations in critically ill patients treated with continuous dosing following a loading dose. With the dosing schedule used, the target set to reach 5× MIC of *P. aeruginosa* during the entire continuous infusion from 1 h after the start of treatment could not be attained. Very low levels were rare. From a pharmacokinetic point of view, continuous dosing is more advantageous than intermittent dosing. However, optimising this dosing strategy merits further attention, as shown by the current data. Depending on which target is to be met, a larger initial cumulative dose is desirable, combined with TDM, to avoid subtherapeutic drug concentrations. Formal proof-of-effect of antibiotic concentrations on survival in randomised controlled studies is still lacking, but it seems both logical and feasible to try to achieve optimal dosing.

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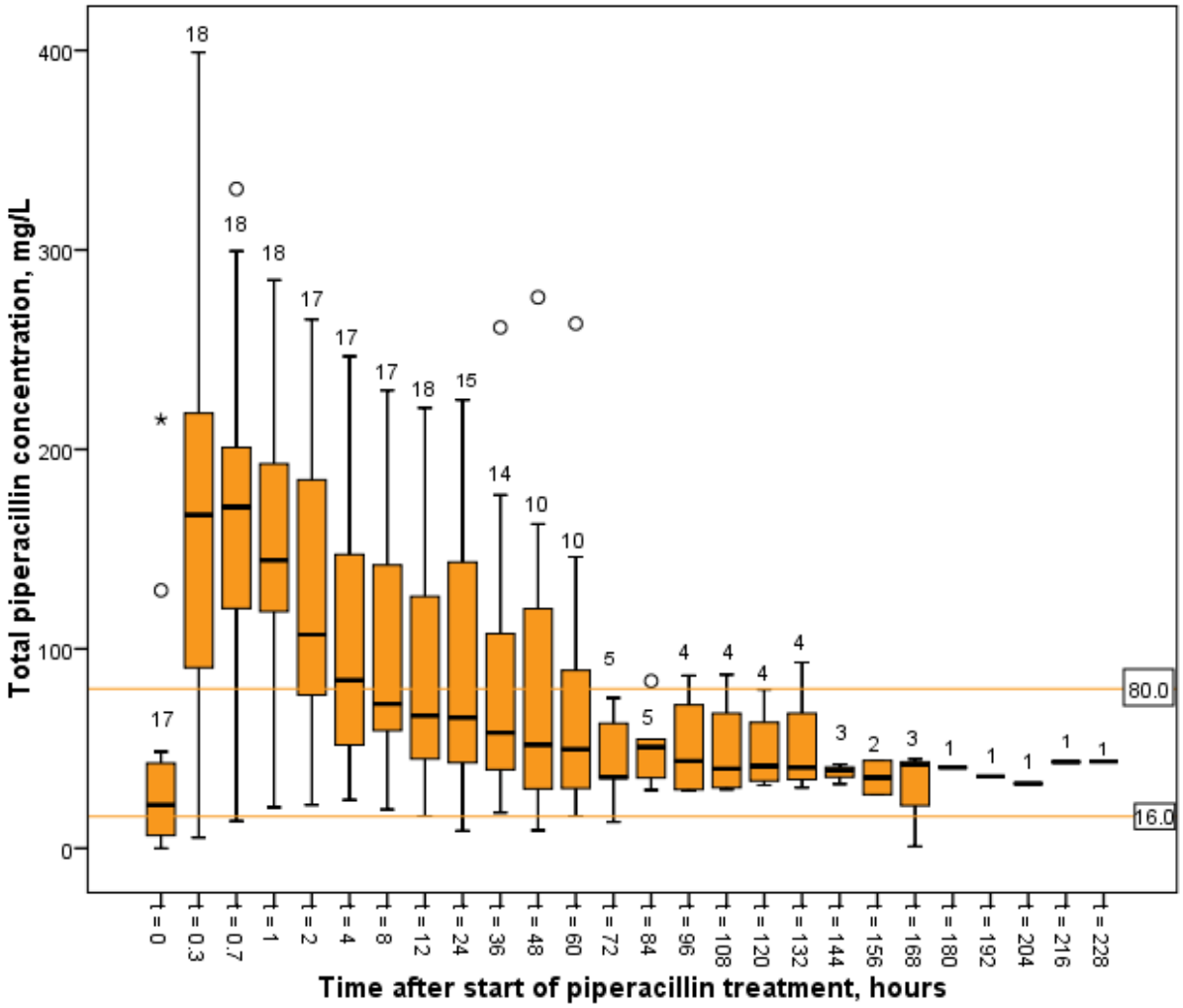
Fig. 1 Total piperacillin concentration over time, from the start of treatment, group level.



Dark line middle of box = median; whiskers represent 1.5 × IQR; circles represent outliers between 1.5–3 × IQR; star represents outlier >3 × IQR; horizontal lines (16 mg/L and 80 mg/L) represent target concentrations discussed in text. The number of data used per boxplots is given above the respective boxplot. IQR, interquartile range.

Table 1 Baseline characteristics and clinical outcome data of patients include in the study (*n* = 18)

Variable	Median [IQR] {range} or *n* (%)
Age (years)	61.5 [54–66.3] {19–72}
Male sex	14 (77.8)
BMI (kg/m^2)	25.1 [22.6–29.7] {21.6–41.2}
Patient category	
Medical	6 (33.3)
Surgery	10 (55.6)
Trauma	2 (11.1)
Presumed/proven site of infection	
Intra-abdominal	12 (66.7)
Respiratory	3 (16.7)
Skin/soft tissue	1 (5.6)
Unknown	2 (11.1)
Co-morbidities [a]	
None	5 (27.8)
Solid malignancy	6 (33.3)
Haemato-oncology	1 (5.6)
Cardiovascular	6 (33.3)
Chronic pulmonary	2 (11.1)
Inflammatory bowel disease/diverticulitis	2 (11.1)
Cushing's syndrome	2 (11.1)
Liver cirrhosis	1 (5.6)
Diabetes	1 (5.6)
APACHE IV score [b]	64 [56–85] {24–128}
Mechanical ventilation	16 (88.9)
Use of vasopressors	17 (94.4)
Measured CL_{Cr} (mL/min) [c]	62.5 [26.8–116.8] {3.4–183.8}

ICU length of stay (days)	9 [3–13.3] {2–75}
ICU mortality	4 (22.2)
Hospital mortality	4 (22.2)

IQR, interquartile range; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; CL_{Cr}, creatine clearance; ICU, intensive care unit.

[a] More than one variable per patient possible.

[b] Available in 13 patients.

[c] Available in 13 patients.

Table 2 Total piperacillin concentration (mg/L) from 1 h after the start of treatment (maintenance phase) and target attainment

	N (% of 172 samples)	*N* (% of 18 patients)	Median	Interquartile range
Follow-up (h) [a]			60	33–96
Concentration (*n* = 172 samples) (mg/L)			65.7	4.9–131.8 Total range, 8.7–284.9
C_{max} (*n* = 18 patients) (mg/L)			144.5	119.4–217.3
C_{min} (*n* = 18 patients) (mg/L)			46.2	28.7–87.2
C ≥ 80 mg/L from 1 h after start of treatment	73 (42.4%)			
C > 16 mg/L from 1 h after start of treatment	168 (97.7%)			
% of samples with *C* ≥ 80 mg/L from 1 h after start of treatment, per patient (*n* = 18)			39.6	15.5–100
% of samples with *C* ≥ 16 mg/L from 1 h after start of treatment, per patient (*n* = 18)			100	100–100
C ≥ 80 mg/L reached within 1 h after start of treatment		16 (88.9%)		
C > 16 mg/L reached within 1 h after start of treatment		18 (100%)		
C ≥ 80 mg/L reached within 1 h after start of treatment AND persistent *C* ≥ 80 mg/L from 1 h after start of treatment		5 (27.8%)		

C > 16 mg/L reached within 1 h after start of treatment AND persistent *C* ≥ 16 mg/L from 1 h after start of treatment		15 (83.3%)		
0% of samples *C* ≥ 80 mg/L from 1 h after start of treatment, per patient (*n* = 18)		2 (11.1%)		
0% of samples *C* ≥ 16 mg/L from 1 h after start of treatment, per patient (*n* = 18)		0 (0%)		

C_{max}, maximum concentration; C_{min}, minimum concentration; *C*, concentration.

[a] Duration of treatment with piperacillin, including sampling of piperacillin concentrations per protocol.