International Journal of Antimicrobial Agents 50 (2017) 68–73

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

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

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ARTICLE INFO

Article history:
Received 1 November 2016
Accepted 22 February 2017

Keywords:
Continuous dosing
Piperacillin
β-Lactam
Critical care

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 (fT) 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

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http://dx.doi.org/10.1016/j.ijantimicag.2017.02.020
0924-8579/

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 4 g/0.5 g 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]. *P. 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%$T_{\geq 5 \times MIC}$ (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 the 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%$T_{>1 \times MIC}$, 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 to 80 mg/L for piperacillin with a correlation coefficient of 0.99941. Within-run coefficient of variation (CV) ranged from 2.5 to 12.9% and between-run CV ranged from 5.9 to 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