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Compliance of extended infusion of piperacillin/tazobactam with the desired pharmacokinetic/pharmacodynamic index in septic patients

Usklađenost produžene primene infuzije piperacilina/tazobaktama sa željenim farmakokinetičkim/farmakodinamskim indeksom kod septičnih bolesnika

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Abstract

Background/Aim. Piperacillin (PIP)/tazobactam (TAZ) – PIP/TAZ is a beta-lactam antibiotic used to treat Gram-negative sepsis. The portion of the dosing interval during which antibiotic concentrations are above the minimal inhibitory concentration – MIC (fT>MIC) or, even more, four times higher than the MIC (fT>4xMIC), represents the pharmacokinetic indices that best correlate with the clinical outcome. In light of the increasing resistance of bacteria in intensive care units (ICUs), it is important to examine the pharmacokinetic/pharmacodynamic (PK/PD) indices of different PIP/TAZ dosing regimens to determine whether this condition is met. The aim of this study was to analyze the efficacy of prolonged intermittent infusion of PIP/TAZ in patients with sepsis in the ICU to achieve the desired PK/PD index. **Methods.** A prospective, controlled, non-interventional study included patients with abdominal post-operative sepsis. Patients received PIP/TAZ in a dose of 4.5 g every 6 hrs in an extended (60-min) intermittent infusion in a daily therapeutic dose of 18 g as part of the prescribed therapy. Blood samples were collected during the first 36 hrs, and antibiotic concentrations were determined using high-performance liquid chromatography. The analysis included the most common isolates from the blood culture in the ICU that were sensitive to PIP/TAZ, and the MICs were also taken from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database. The primary objective of the PK/PD study was to determine the indices fT>MIC and fT>4xMIC as the best indicators of therapeutic efficacy. For the pharmacodynamic target, this period was determined to be ≥ 50% of the time of the dosing interval. **Results.** The maximum achieved PIP concentrations in examined patients were 130.03 ± 32.43 μg/mL. Based on PK/PD data, the applied PIP/TAZ dosing regimen was effective against sensitive strains whose MIC did not exceed 16 μg/mL (fT>MIC = 56%). If we take fT>4xMIC≥50% as a target value, that percentage was significantly below the set goal (27%). For strains that include strains with a phenotypic resistance mechanism, PK/PD values for fT>4xMIC≥50% were far below the set goal (2–11%), except for *Escherichia coli* (79%). **Conclusion.** An intermittent 60-min infusion of PIP/TAZ meets the required pharmacodynamic target fT>MIC≥50% for sensitive strains of bacteria with an interruption point from 16 μg/mL. The indicated dosing regimen did not meet the target PK/PD values in the case of resistant strains.

Key words:
beta lactam, antibiotics; chromatography, high pressure liquid; drug resistance, microbial; infusion, intravenous; pharmacokinetics; pharmacology; sepsis.

Apstrakt

Uvod/Cilj. Piperacilin (PIP)/tazobaktam (TAZ) – PIP/TAZ je beta laktamski antibiotik koji se koristi u lečenju sepse uzrokovane Gram negativnim bakterijama. Deo intervala doziranja tokom kojeg su koncentracije antibiotika iznad minimalne inhibitorne koncentracije (*minimal inhibitory concentration* – MIC) (fT>MIC) ili značajnije, četiri puta veće od MIC-a (fT>4xMIC), predstavljaju farmakokinetske indekse koji najbolje koreliraju sa kliničkim ishodom. U svetlu sve veće rezistencije bakterija u jedinicama intenzivne nege (JIN), važno je ispitati farmakokinetske/farmakodinamske (*pharmacokinetic/pharmacodynamic* – PK/PD) indekse kod različitih režima doziranja PIP/TAZ, da bi se utvrdilo da li će taj uslov biti ispunjen. Cilj rada bio je da se analizira

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efikasnost produžene intermitentne infuzije PIP/TAZ kod bolesnika sa sepsom u JIN, kako bi se postigao željeni PK/PD indeks. **Metode**. Prospektivnom, kontrolisanom, neintervencijskom studijom obuhvaćeni su bolesnici sa abdominalnom postoperativnom sepsom. Bolesnici su primali PIP/TAZ u dozi od 4,5 g na 6 sati u produženoj (60-min) intermitentnoj infuziji u dnevnoj terapijskoj dozi od 18 g, kao propisanu terapiju. Uzorci krvi uzimani su tokom prvih 36 sati, a koncentracije antibiotika određene su primenom tečne hromatografije visokih performansi. U analizu su uključeni najčešći izolati iz hemokulture u JIN koji su bili osetljivi na PIP/TAZ, a MIC-e su preuzete iz baze *European Committee on Antimicrobial Susceptibility Testing* (EUCAST). Primarni cilj PK/PD studije bio je da se odrede indeksi fT>MIC i fT>4xMIC kao najbolji pokazatelji terapijske efikasnosti. Za farmakodinamski cilj određeno je da taj period bude ≥ 50% vremena intervala doziranja. **Rezultati**. Maksimalna koncentracija PIP kod ispitivanih bolesnika iznosila je 130,03 ± 32,43 μg/mL. Na osnovu PK/PD podataka, primenjeni režim doziranja PIP/TAZ bio je efikasan protiv osetljivih sojeva čija je MIC bila ispod 16 μg/mL (fT>MIC = 56%). Uzimanjem fT>4xMIC≥50% kao ciljne vrednosti, taj procenat bio je značajno ispod cilja (27%). Kod sojeva koji uključuju sojeve sa mehanizmom fenotipske rezistencije, vrednosti PK/PD za fT>4xMIC≥50% bile su značajno ispod postavljenog cilja (2–11%), osim za *Escherichia coli* (79%). **Zaključak**. Intermitentna 60-min infuzija PIP/TAZ ispunjava zahtevani farmakodinamski cilj fT>MIC≥50% za osetljive sojeve bakterija, sa tačkom prekida od 16 μg/mL. Navedeni režim doziranja nije ispunio ciljne PK/PD vrednosti u slučaju rezistentnih sojeva.

Ključne reči:
antibiotici, beta laktamski; hromatografija, tečna, pod vp; lekovi, rezistencija mikroorganizama; infuzije, intravenske; farmakokinetika; farmakologija; sepsa.

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1–3]. The alterations in organ and system functioning during sepsis can significantly affect the pharmacokinetics (PK) and pharmacodynamics (PD) of the administered antibiotic. Fluid extravasation into the interstitial space due to capillary damage and vascular dysfunction, hypoalbuminemia as a consequence of liver function disorders, kidney function disorders in the sense of increased renal clearance or acute renal damage, cardiovascular system dysfunction with great inter-individual variability are only part of the pathophysiological changes that significantly complicate adequate dosing medicines and often require therapeutic monitoring [4–5]. Due to these changes, therapeutic doses of antibiotics may be insufficient to meet the PK/PD target necessary to inhibit the growth of or kill the pathogen, which results in poor therapeutic outcomes [3–5]. Optimizing antibiotic therapy according to PK/PD indices and providing an individualized approach for the treatment of a septic patient is essential for a successful treatment outcome and prevention of antibiotic resistance [6]. The leading PK/PD indices are categorized as follows: the ratio of maximum drug concentration (Cmax) to minimal inhibitory concentration (MIC) (Cmax/MIC); the duration of time that the unbound drug concentration remains above the MIC during a dosing interval (fT>MIC); the area under inhibitory curve (AUIC) – the ratio of the area under the concentration-time curve during 24 hrs to MIC (area under the curve – $AUC_{0–24}$/MIC) [5]. However, the optimal PK/PD target of beta-lactams to achieve clinical cure in microbiological eradication in critically ill patients remains undefined, including decisions for different infusion durations [7].

Achieving PK/PD targets depends on the dose and the duration of administration. Unlike conventional intermittent infusions (infusion ≤ 30 min), administration of extended intravenous (i.v.) infusion, either as an extended infusion (antibiotic infused for at least half of the dosing interval) or as a continuous infusion, results in sustained beta-lactam concentrations consistent with these drugs' PD. The meta-analyses reported similar results, confirming reduced short-term mortality [relative risk (RR), 0.70; 95% confidence interval (CI), 0.57–0.87] with prolonged beta-lactam infusion [8–10]. A prolonged infusion is a feasible intervention if there is an appropriate i.v. access and available resources to ensure that the beta-lactam antibiotic is infused for the required time, which can become a significant problem where resources are limited, particularly in developing countries. However, the randomized international clinical trial BLING III conducted on 7,202 critically ill patients with sepsis who received piperacillin/tazobactam (PIP/TAZ) as intermittent or continuous infusion together with meropenem showed that there was no significant difference in all-cause mortality at day 90: 24.9% (continuous) vs. 26.8% (intermittent), absolute difference -1.9% (95% CI -4.9 to 1.1), odds ratio (OR)- 0.91 (95% CI 0.81 to 1.01), $p = 0.08$. There was no significant difference in all-cause ICU mortality, but clinical cure was significantly better in the continuous infusion group ($p = 0.001$) [11].

One of the most commonly used antibiotics in ICUs is a combination of PIP/TAZ, indicated for the treatment of severe intraabdominal infections mainly caused by *Enterobacterales* [12, 13]. To ensure a good clinical outcome, the leading PK/PD index, the duration of time (T) that the free antibiotic concentration remains above the MIC during a dosing interval (fT>MIC) must be more than 50%; however, expert opinion recommends drug levels of even 4–5xMIC for 100% of the dosing interval for critically ill patients with variable PK/PD parameters [14–16]. The recommended dose of PIP/TAZ (according to the summary of product characteristics – SmPC) for the treatment of severe infections is 4.5 g, which is administered every 6 hrs by intermittent i.v. infusion over 30 min [electronic medicines compendium (EMC), 2023] [17]. In recent documents, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [18] and the Food and Drug Administration (FDA) [12] recommend administering a 30-min or extended 3-hr infusion. However, recently pub-

lished research mentions the administration of PIP/TAZ in continuous infusion, which, according to the authors, achieves the longest time when the values are above the MIC [19]. These differences in recommendations often cause clinicians difficulty when deciding on the dosing regimens.

Rates of resistant pathogens are generally higher in the ICU compared to general hospital wards due to the use of broad-spectrum antibiotics, transmission within the ICU, and patients requiring invasive procedures [20]. Resistant pathogens present a challenge to PD, with elevated MICs requiring higher antibiotic concentrations to achieve an equivalent PK/PD target. Therefore, we analyzed the cut-off points of both sensitive strains of the most common causal bacteria of sepsis in the ICU and cut-off points that include 90% of all strains, both sensitive and those with some phenotypic resistance mechanisms, for the most common sepsis-causing bacteria (MIC_{90}) from the database EUCAST [18].

An official recommendation is the use of PIP/TAZ in an intermittent infusion over 30 min, and the existing studies favor the use in the form of prolonged or continuous infusion. In many clinical centers in developing countries, there is no possibility of administering antibiotics by the pump as a continuous or prolonged infusion, and a 60-min infusion is used in seriously ill patients. Therefore, this research aimed to study the effect of a 60-min infusion of a high-dose regimen of PIP/TAZ in patients with sepsis and septic shock in the ICU in the context of achieving the desired PK/PD parameters.

Methods

Setting

This prospective, controlled, non-interventional study was conducted in the University Clinical Center of Vojvodina ICU in Novi Sad, Serbia. PD measurements were conducted at the Faculty of Medicine in Novi Sad, Department for Pharmacology and Clinical Pharmacology. The approval for conducting the study was obtained from the Ethics Committee of the University Clinical Center of Vojvodina (No. 00-20/610), with written informed consent from either the patient or the patient's nominated substitute decision-maker.

Patients

The study was performed on patients who met the inclusion criteria. The sufficient number of subjects was 13 to assess the relationship between fT>MIC and fT>4xMIC for the required $r > 0.7$, the statistical power of 80%, and a $p \leq 0.05$. Patients were eligible for enrolment if they were between 18 and 80 years of age, had *post*-surgical abdominal sepsis (AS) [Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II)], were hospitalized in the ICU, and were receiving prescribed PIP/TAZ as a part of the protocol for the treatment of sepsis. Exclusion criteria were as follows: patients who did not have an intraarterial line inserted as part of routine management or if the blood could not be obtained for another reason (to allow repeated plasma sampling without additional venipuncture); patients who had renal impairment (defined by a plasma creatinine concentration greater than 171 μmol/L) or who required renal replacement therapy; patients with a history of allergy to PIP; patients who decided not to participate in the study. The patient flow chart is shown in Figure 1.

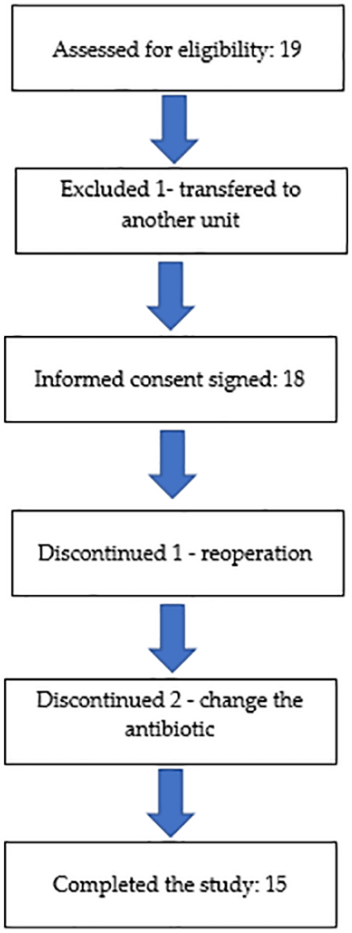

Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) flow chart of the patients.

Duration of the study

The inclusion period lasted 12 months (January 1 to December 31, 2019), which was necessary to collect sufficient participants. After inclusion in the study, we took the first sample, and after the first administration of PIP/TAZ, blood samples were taken for 36 hrs for PD analysis. In our sample of patients, we monitored mortality over 28 days from the start of the study.

Drugs

PIP/TAZ 4 g/0.5 g powder for solution for infusion was used. Each vial contains 4 g PIP (as sodium salt) and 0.5 g TAZ (as sodium salt).

PIP/TAZ was administered immediately after the diagnosis of sepsis as an intermittent 60-min i.v. infusion at a daily dose of 18 g, 4.5 g every 6 hrs.

Measurement of the concentration of piperacillin

A blood sample was obtained *via* venipuncture from the patients during the first 36 hrs of therapy. Samples were taken on the first day eight times after the first dose (15 min, 30 min, 60 min, and 1, 2, 3, 4, and 6 hrs). Afterward, blood was sampled before each subsequent dose and 10 min after the end of infusion (dose) until 36 hrs. The samples were obtained for 36 hrs, as we wanted to cover the concentrations after the first dose and at a steady state.

The amount of blood taken during individual sampling without coagulation was 1 mL. We stored serum samples at -20 °C until analysis.

The concentration of total PIP was determined using high-pressure liquid chromatography (HPLC) (Dionex, USA) with ultraviolet detector, according to the method of Rama Krishna et al. [21]. In the case of PIP, the free fraction is 70% of the total concentration, and based on that, we calculated the concentration of free PIP in the blood [22].

From the PK parameters, we calculate the Cmax, Cmin, and AUC_{0-24} μg/mL × hr and AUC_{24-36} μg/mL × hr using the PK Solver program (add-in program for Microsoft Excel, Microsoft Corporation, USA) [23].

Microbiological assay

The most frequently isolated bacteria from ICU patients with AS were used to calculate PK/PD parameters. The MIC value was determined using the EUCAST epidemiological cut-off values (ECOFF) breakpoint for the most susceptible strains of pathogens [18].

We used the EUCAST ECOFF databases for sensitive strains [18] as MIC breakpoints for the tested strains of bacteria. We also determined the MIC_{90}, which includes 90% of all reported strains, both those with and without phenotypically detectable acquired resistance mechanisms (non-wild type). We took all strains into account due to the high level of resistance of pathogens present in the ICU units.

Calculation of pharmacokinetic/pharmacodynamic indices

The primary endpoint investigated in this study was to calculate the PK/PD indices. We calculated two PK/PD indices as the best indicators of the effectiveness of therapy: %fT>MIC and AUIC.

The percentage of time during which the unbound concentration of PIP remains above the MIC for the analyzed bacterial strain (%fT>MIC) represents the PK/PD index associated with optimal PIP/TAZ activity. This index was defined as fT>MIC≥50%, which is also considered the PD target (PDT) [24]. However, data from critically ill patients suggest that patients may benefit from longer contact (e.g., 100% fT>MIC) [5, 25] with higher concentrations (e.g., 2–5 x MIC) [26] of beta-lactam antibiotics than those previously described. Therefore, when calculating the PK/PD index, we also calculated the ratio of the dosing interval during which the unbound PIP was higher than 4 x MIC (fT>4xMIC).

AUIC is a measure of the area under the concentration-time curve for 24-hr dosing/MIC (AUC_{0-24}/MIC). As previously described, target values for AUIC are 125–500, as evaluated for beta-lactam, with a target breakpoint stated as the value of 125. However, even higher values of 250 are needed for optimal treatment [27].

Statistical analysis

The data were presented in tables and graphs and evaluated using descriptive statistics (mean values and standard deviations).

The Mann-Whitney *U* test (with a threshold of $p = 0.05$) was used to determine a statistically significant difference between the mean PIP concentrations and the measured values fT>MIC and fT>4xMIC.

Results

Study sample

A total of 19 patients were assessed for eligibility. One was excluded due to a transfer to another unit. Eighteen patients signed informed consent. Two were excluded due to a change of antibiotics, and one was excluded due to reoperation. Finally, a total of 15 patients were included, hence total number of patients who completed the study was 15 (9 men and 6 women) (Figure 1). The average age of the respondents was 68.90 years, and the average body weight was 85.43 kg (Table 1). We used the SOFA and APACHE II scores as a criterion for sepsis diagnosis (Table 2). The 28-day mortality was 47.62%.

The most common bacterial isolates

The most common bacterial isolates from the patients with postoperative AS sensitive to PIP/TAZ at the ICU department were *Klebsiella pneumoniae*, *Escherichia coli (E. coli)*, *Pseu-*

Table 1

Demographic characteristics of the 15 patients with sepsis who received prolonged intermittent infusion of PIP/TAZ in the ICU.

Sex	n (%)	Age, years	Weight, kg
Men	9 (60)	66.41 ± 12.89	92.44 ± 18.02
Women	6 (40)	72.54 ± 11.50	72.80 ± 17.06
Total	15 (100)	68.90 ± 14.04	85.43 ± 19.90

PIP/TAZ – piperacillin/tazobactam; ICU – intensive care unit.
Values are given as numbers (percentages) or mean ± standard deviation.

domonas aeruginosa, and *Enterobacter spp.* (Table 3). Likewise, sporadically isolated but resistant to PIP/TAZ were *Clostridium tetani, Enterococcus faecium, Acinetobacter spp.*, and coagulase-negative *Staphylococcus.*

Pharmacokinetic calculation of piperacillin

We determined the AUC values of PIP for the first 24 hrs ($AUC_{0–24}$ = 1,141.12 μg/mL x hr) and the period 24–36 hrs ($AUC_{24–36}$ = 1,568.96 μg/mL x hr). The mean value of the Cmax for the applied dosing regimen was 130.03 μg/mL (Table 4). The highest concentrations ranged between 125 μg/mL and 132 μg/mL, while the lowest concentrations, obtained immediately before administering the next dose, were as low as 2.4 μg/mL and 2.8 μg/mL.

The calculated ratio of the free fraction of PIP concentrations/time curves and the MIC for the most common bacterial pathogens isolated from patients with sepsis is shown in Figure 2. The chart represents the basis for determining the PK/PD parameters.

Table 3 shows the MIC and MIC_{90} values [18] for the most common isolates sensitive to PIP. For each strain, PK/PD indices (fT>MIC and fT>4xMIC) based on PK data of PIP and PD values (MIC) of the causative agent are presented. We calculated the AUIC ($AUC_{0–24}$/MIC) ratio for the analyzed strains. Table 3 also shows the breakpoint of sensi-

Table 2

The values of APACHE II and SOFA scores in septic patients at the beginning of the study

Scores	Value
SOFA	6.93 ± 4.11
APACHE II	22.43 ± 19.65

SOFA – Sequential Organ Failure Assessment; APACHE – Acute Physiology and Chronic Health Evaluation.
Values are given as mean ± standard deviation.

Table 3

Calculation of PK/PD indices the most common sensitive isolates from blood culture in the ICU from the MIC and concentration/time curve of unbound piperacillin in the blood

Bacteria (% prevalence)	MIC (μg/mL) (EUCAST)	fT>MIC	fT>4xMIC	$AUC_{0–24}$/MIC (AUIC)	Breakpoint for PK/PD (fT>MIC≥ 50%)#
Klebsiella pneumoniae	8*	79 (67–81)	27 (22–31)	143	
(33.3)	64**	11 (8–14)	0	18	
Escherichia coli	8*	79 (67–81)	27 (22–31)	143	
(16.6)	8**	79 (67–81)	27 (22–31)	143	16 μg/mL
Pseudomonas aeruginosa	16*	56 (43–67)	11 (8–14)	71	
(5.6)	128**	2 (0–5)	0	9	
Enterobacter spp.	8*	79 (67–81)	27 (22–31)	143	
(5.6)	128**	2 (0–5)	0	9	

PK/PD – pharmacokinetic/pharmacodynamic; ICU – intensive care unit; MIC – minimal inhibitory concentration; EUCAST – European Committee on Antimicrobial Susceptibility Testing; fT>MIC – time period during which unbound drug concentration remains above the MIC; fT>4xMIC – time period during which unbound drug concentration remains above 4 times the MIC; AUC – area under the curve; AUIC – area under the inhibitory curve.
The fT>MIC and fT>4xMIC values are presented as mean (minimum-maximum) in percentages.
sensitive strains (without acquired resistance – EUCAST [18]); *MIC_{90} covering 90% of strains without and with a phenotypically detectable mechanism of resistance, calculated from EUCAST bases [18]; # – [13, 18, 23].**

Table 4

Pharmacokinetic parameters (AUC, Cmax, Cmin) of the free fraction of piperacillin in blood samples after 4 g/6 hr intravenously administration for 60 min, for 36 hrs

Pharmacokinetic parameter	Values
AUC_{0-24}, μg/mL × hr	1,141.12 ± 61.87
AUC_{24-36}, μg/mL × hr	1,568.96 ± 398.48
$AUC_{0-\infty}$, μg/mL × hr	3,062.25 ± 622.37
Cmax, μg/mL	130.03 ± 32.43
Cmin, μg/mL	2.60 ± 0.17

AUC – area under the curve; Cmax – maximum drug concentration; Cmin – minimum drug concentration.
Values are given as mean ± standard deviation.

tivity for the PK/PD indices based on literature data. The breakpoint for the PD target is defined based on literature data as 16 μg/mL (Figure 3). While for the sensitive strains of bacteria, the time above the MIC was 79%, concentrations of PIP 4xMIC were present for only 27% of the dosing interval. The PIP concentrations were lower than the 4xMIC for all dosing intervals for strains with a phenotypic resistance mechanism. We got the same results when calculating AUIC ($AUC_{0–24}$/MIC). For sensitive strains of bacteria, the $AUC/MIC_{0–24}$ ratio was higher than 100. It was as low as 9–18 for resistant bacteria, except for *E. coli* (143).

We found a statistically significant correlation between the mean PIP concentrations and the measured values of fT>MIC and fT>4xMIC ($r = 0.97$; $p = 0.001$).

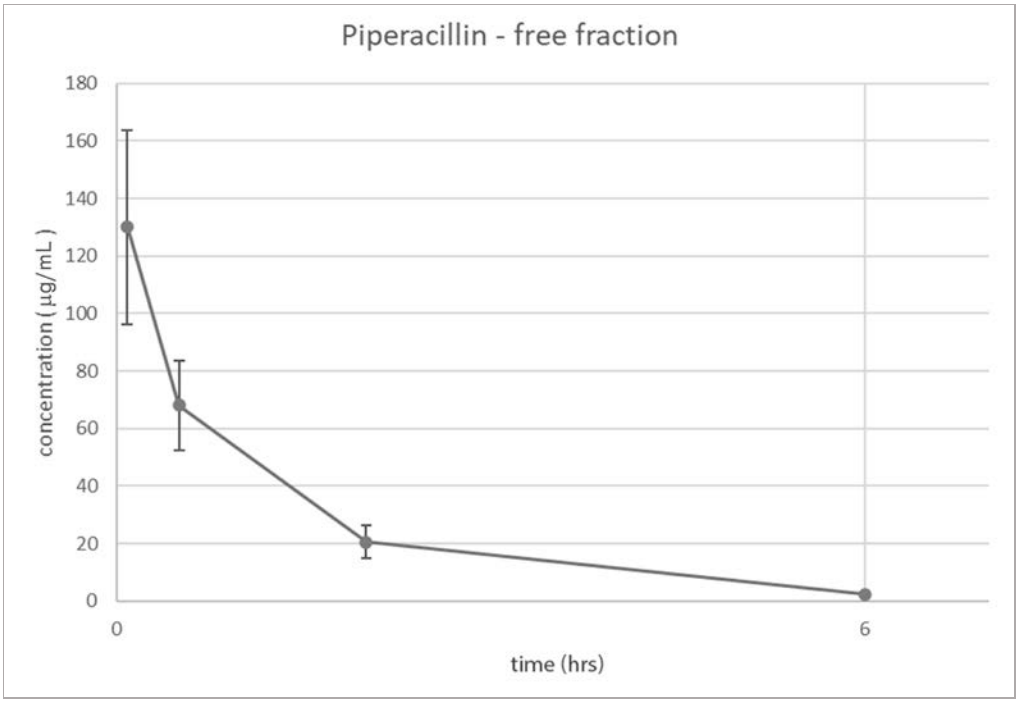

Fig. 2 – The ratio of the free fraction of piperacillin concentrations (μg/mL)/time curves for the first 6 hrs after administration of 4.5 g intravenously for 6 hrs. Values are given as mean ± standard deviation.

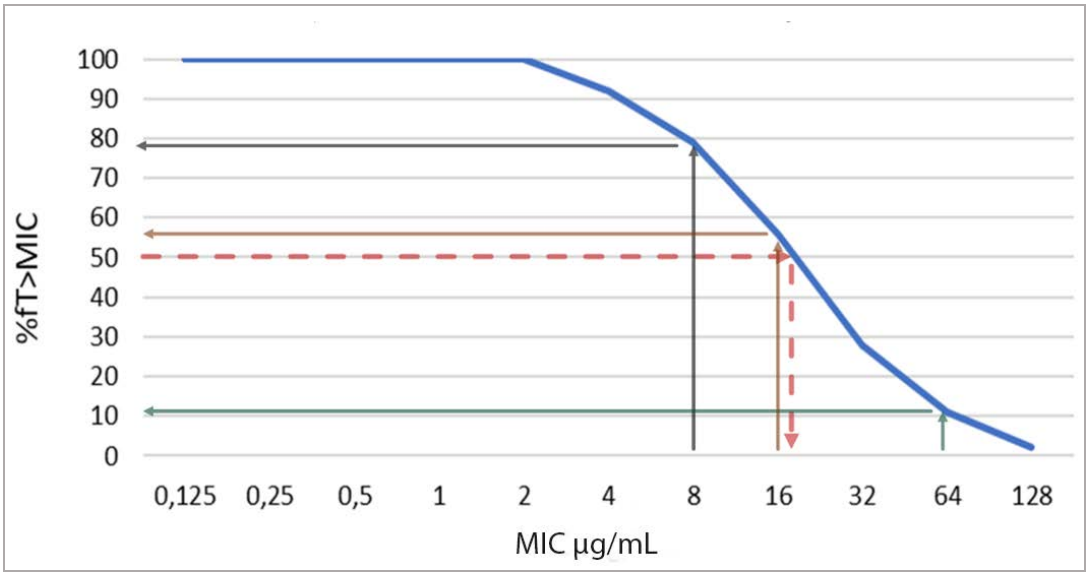

Fig. 3 – Relationship between fT>MIC and MIC of piperacillin/tazobactam, 4.5 g administered intravenously for 60 min. Assuming the pharmacodynamic target of fT>MIC≥50%, the cut-off point is 16 μg/mL (dashed arrows). The fT>MIC values are also marked, which are shown by solid arrows for MIC = 8 μg/mL (79%), MIC = 16 μg/mL (56%), and MIC = 64 μg/mL (11%). More detailed data are presented in Table 4.

MIC – minimal inhibitory concentration; fT>MIC – time period during which unbound drug concentration remains above the MIC; %fT>MIC – percentage of time period during which unbound drug concentration remains above the MIC.

Discussion

In everyday practice, real problems often require a different approach to assessing the PK/PD profile of antibiotics in septic patients, which can significantly reduce the accuracy of calculations. Given that in the first 24–48 hrs of sepsis treatment, which are considered crucial for the treatment outcome, it is not realistic to obtain microbiological analyses that confirm the identity and sensitivity of the causative agent (MIC), we are forced to use EUCAST [18] data or our own database. In this sense, this work is an example of the only possible PK/PD approach in many environments if this type of therapy evaluation is to be done.

In our study, a high-dose regimen of PIP/TAZ administered by partially extended intermittent administration (60 min) enabled the achievement of an average fT>MIC value of 79% for sensitive strains of three out of four most common pathogens (*Klebsiella*, *E. coli*, and *Enterobacter*), which suggests the possibility of successful clinical outcome. For *Pseudomonas*, the higher MIC breakpoint value of 16 μg/mL for susceptible strains shows fT>MIC of 56% within the set PDT. However, when considering fT>4xMIC, the period during which the concentrations were four times above the MIC value, even in susceptible strains with lower MIC values (8 μg/mL), was only 27%, which is significantly less than the target values (50%). AUIC values were correlated with fT>MIC values for susceptible strains and reached a value of 143, which is above the limit of 125.

In strains that include microorganisms with a phenotypic resistance mechanism, only in *E. coli*, the MIC_{90} value of 8 μg achieves PDT (fT>MIC≥50%) due to the large number of strains with low MIC. In other pathogens, their high MIC_{90} values (64–128 μg) resulted in low fT>MIC (2–11%) and AUIC (9–18) values, far below what is needed to achieve the desired goal.

PK/PD calculation suggests that intermittent dosing can achieve target exposures comparable to continuous infusion when pathogen MICs are low; however, in the presence of less susceptible pathogens, intermittent dosing is associated with a higher risk of treatment failure [28]. Intermittent dosing produces PIP concentrations below the MIC for most dosing intervals when pathogens with phenotypic resistance mechanisms are involved.

According to our results, the applied intermittent dosing, although lasting 60 min (16.6% of the dosing interval), was not sufficient to provide optimal PK/PD parameters (fT>4xMIC), which some authors state as minimum targets when it comes to severe infections [14, 15].

Following these results, using the PIP/TAZ combination in severe infections is accompanied by controversial conclusions related to the clinical outcome of therapy. According to one group of authors, there were no statistical differences in cure rates between the two treatment arms (continuous or conventional intermittent dosing) and no adverse events [29, 30]. Furthermore, the meta-analysis showed that therapeutic drug monitoring (TDM)-guided dosing of beta-lactam antibiotics improved clinical and microbiological cure but did not reduce mortality or length of stay [31]. According to recent studies, PIP/TAZ given *via* continuous/prolonged infusion [10, 24] improved clinical outcomes in critically ill patients. However, in our trial, it is evident that the investigated dosing regimen of PIP/TAZ is insufficient to achieve the target exposure of unbound PIP plasma concentration above the MIC for most of the dosing interval (100% fT>MIC) to ensure 40% to 70% of fT>4xMIC, as suggested by some authors for severe infections [32]. Although the investigated dose regimen failed to achieve PDT (50% fT>4xMIC) for most bacteria, including those with some phenotypic resistance mechanism, the predictive significance of the PK/PD index on the final treatment outcome of patients with sepsis remains an open question, in the context of recently published studies [31].

The next issue involves the guidelines for the use of antibiotics. When writing the SmPC as an official document for the administration of antibiotics, manufacturers follow the results of the tests carried out when they are introduced and placed on the market, which can, over time, result in decreased clinical outcomes [33]. However, individual patient differences cannot be considered when writing the guidelines, especially in sepsis. Antibiotic concentrations vary multiple times due to pathophysiological changes. Constant changes in MICs for pathogens are another factor that must be constantly considered [34]. Therefore, the application method should be strictly individualized (TDM, MIC, individual calculation of PK/PD parameters). However, especially in areas that do not have optimal conditions for this, this happens very rarely.

In most cases, doctors prescribe antibiotics according to the dosage instructions, not having enough time and opportunity to devote to each patient. This leads to unsatisfactory results in patients with a low PK profile (lower than average concentrations of PIP). This may be one of the main reasons the applied dosing regimens in critical patients failed to achieve the desired therapeutic outcome. Therefore, the assessment of the PK profile of each patient and the adjustment of the administration regimen could be associated with a different, optimal dosing regimen for such a subgroup of patients, ultimately leading to a better therapeutic outcome.

Limitations of the study

The study had several limitations. First, the research subjects were selected from a single center, which limited the size of the sample. Second, the negative microbiological samples in a number of participants, as well as the period for waiting for the microbiological samples, 3–5 days, which forced us to use the most common pathogens isolated from patients with postoperative AS in the ICU rather than individual microbiological results, are also limiting factors for the study. Future studies with larger sample sizes across all cohorts are needed to confirm these findings.

Conclusion

The obtained PK/PD parameters support the fact that with intermittent infusion, it is possible to achieve the PK/PD

goal (fT>MIC≥50%) for susceptible pathogens (breakpoint MIC ≤ 16 μg/mL). When including causative agents with phenotypic resistance mechanisms, the tested PIP/TAZ dosing regimen does not meet the PK/PD parameters, except in the case of *Escherichia coli*. Achieving the PK/PD target in treating severe infections (fT>4xMIC>50%), such as sepsis, with a given PIP/TAZ dosing regimen for the analyzed agents remains elusive. For this reason, administration of PIP/TAZ as a high-dose continuous infusion should be considered.

Conflict of interest

The authors declare no conflict of interest.

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