CURRENT TOPIC

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Beta-lactam antibiotics use in intensive care units – The pathophysiological, pharmacokinetic, pharmacodynamic and pharmacoeconomic approach

Upotreba beta-laktamskih antibiotika u jedinicama intenzivne terapije – patofiziološki, farmakokinetički, farmakodinamički i farmakoekonomski pristup

Aneta Perić*†, Maja Šurbatović†‡, Sandra Vezmar Kovačević§, Mirjana Antunović*†, Milić Veljović†‡, Ivana Krstić-Lečić‡, Dragan Djordjević†‡, Vesna Kilibarda†‖, Snježana Zeba†‡, Silva Dobrić†¶

***Sector for Pharmacy, ‡Clinic of Anesthesiology and Intensive Therapy, ‖National Poison Control Center, ¶Institute for Scientific Information, Military Medical Academy, Belgrade, Serbia; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; §Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia**

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Introduction

Sepsis, as a systematic inflammatory response to infection, compromises a number of very complex pathophysiological processes: diffuse endothelial and epithelial injury, increased capillary permeability, impaired hemodynamics, microvascular thrombosis, tissue ischemia, apoptosis and can result in multiple organ dysfunction [1–4]. It is one of the most frequent reasons for intensive care hospitalization. It is estimated that the mortality in severe sepsis patients ranges from 40% to 70%. Moreover, it is the second leading cause of death among patients in non-coronary intensive care units (ICUs) and the tenth leading cause of death overall in the United States [5, 6]. Several recent studies suggest that the mortality rate from severe sepsis is not changed remarkably over the last 30 years. During that time, the incidence of sepsis has been increasing [6]. The mean hospital cost *per* patient was estimated at $22,100 [7]. Vincent et al. [8] studied patients admitted to ICUs all over Europe and found that ICU mortality was almost doubled among patients with sepsis compared to those without sepsis, 27% *vs* 14%, respectively. ICU mortality rate from severe sepsis and septic shock was even higher, 32.2% and 54.1%, respectively. These results are from SOAP study in which our ICU (Clinic of Anesthesiology and Intensive Therapy of the Military Medical Academy, Belgrade, Serbia) participated. The results from the most populous country, China, showed that the overall hospital mortality from severe sepsis was 48.7%. The mean hospital cost was $11,390 *per* patient and $502 *per* patient *per* day [9]. Even if patients survive sepsis, their quality of life is expected to be substantially reduced [5, 6].

The cornerstones for the therapy of sepsis are aggresive fluid resuscitation, source control, and antimicrobial treatment. Antimicrobial agents are one of the frequently utilized drug classes in an ICU [5, 10]. The results of previous investigations showed that antibiotic treatment decreases the concentrations of inflammatory mediators in body fluids [11, 12]. However, in patients with sepsis the rapid clinical deterioration is often seen after the first dose of cidal antibiotics. This phenomenon could be explained with Jarish-Herxheimer reaction (JHR), which is a syndrome with worsening of symptoms immediately after antimicrobial treatment of infection. It is caused by the production of higher inflammatory mediators [2]. Selecting an appropriate antimicrobial in terms of spectrum of activity is the mainstay of antimicrobial therapy. Still, the consistent choice of correct dosage regimen (in terms of both dose and frequency of administration) has been shown to be at least as important for successful clinical cure and microbiological eradication as the choice of drug [13, 14]. Empirical treatment of bacterial infections in an ICU is based

Correspondence to: Aneta Perić, Sector for Pharmacy, Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. Phone: +381 11 3609 225. E-mail: aneta.peric@gmail.com

predominantly on the identification and susceptibility of bacteria commonly isolated in that unit [10, 15]. It has been demonstrated that inappropriate use of antibiotics causes an enhancement of antimicrobial resistance. This contributes significantly towards elevated health care costs and patient morbidity and mortality [16–18]. Optimized exposure to antimicrobials has been shown to result in improved clinical outcomes [13].

Besides, pathophysiological changes due to systematic inflammatory response may markedly alter pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs [19]. Due to this dosage of antibacterial drugs in critically ill patients is not straightforward. However, newer data suggest that antibiotic stewardship programs lead to the reduction in duration of hospital stay and saving in medical expenses [17, 20].

Among numerous antibacterial agents, carbapenems, a group of β-lactam antibiotics with a broad spectrum of activity, are considered to be the first-line empirical antibiotic therapy in critically ill patients. They exibit *in vitro* bactericidal activity against numerous pathogens, including Gram-positive and Gram-negative aerobes and anaerobes, but lack activity against *Enteroccocus faecium*, methicillin-resistant *Staphylococcus aureus* and *Stenotrophomonas maltophilia*. Currently, most often used carbapenems in clinical practice are: imipenem, meropenem, ertrapenem and doripenem. Doripenem and meropenem possess a slightly more potent anti-pseudomonal activity compared to imipenem, while ertrapenem lacks activity against *Pseudomonas aeruginosa* and *Enterococcus* spp. Imipenem, meropenem and doripenem have half-lives of approximately 1 hour, while ertrapenem displays a high protein binding and has the half-live of approximately 4 hours, making it suitable for once-daily administration. Imipenem is susceptible to degradation by enzyme dehydropeptidase-1, and requires co-administration of cilastatin. Ertrapenem is more suitable for the treatment of community-acquired infections and outpatient intravenous antimicrobial therapy. Imipenem and meropenem are used in treatment of moderate to severe nosocomial and polymicrobial infections [21–26].

Considering all of the above, the aim of this study was to review studies with PK and PD concepts in order to get data about the appropriate dosing regimen of carbapenems in critically ill patients with sepsis, having into account specific pathophysiological changes in these patients.

Antibiotic pharmacokinetic/pharmacodynamic considerations in critically ill patients

Critically ill patients receive multiple medications from a variety of pharmacological classes due to the life threatening illness. They are a unique population with diverse disease processes, existing or impending multiple organ dysfunction and altered PK and PD characteristics to which pharmacotherapy is added [27]. PK changes can be the result of organ dysfunction, most notably the liver and kidneys, but can also be a consequence of the acute phase response, drug interactions and therapeutic interventions [28].

Pathophysiology of sepsis in critically ill patients

The pathophysiology of sepsis is complex. Activation of inflammatory cytokine and coagulation cascades are important features of its pathogenesis and strongly influence pharmacokinetic properties of administered medication. Cytokines have the central role in positive and negative regulation of immune responses and in integrating these reactions with other physiological systems, such as the complement and hematopoietic systems. The effect of cytokines *in vivo* varies depending on time and location. They can be classified into proinflammatory [(T helper, Th1; i.e. tumor necrosis factor-(TNF)-α, interleukin-(IL)-1; anti-inflammatory Th2 cytokines; i.e. IL-10, and Th17, different from both Th1 and Th2)]. Some possess both activities, i.e. IL-6. Circulating levels of both proinflammatory and anti-inflammatory cytokines can be either eleveted or decreased in sepsis [29, 30]. They act by binding to specific receptors at the target cell membrane, setting off a cascade that leads to introduction, enhancement, or inhibition of a number of cytokine-regulated genes in nucleus, thereby modulating cytokine-regulated activity of cells. There is a great variability seen in the clinical profile and outcome in patients who encounter similar insults like trauma and/or infection. Now research is focused on genetic determinants of the immunoinflamatory response [31].

Pharmacokinetic changes in critically ill patients

Increase in the volume of distribution (Vd) is common primarily due to the expansion of the extracellular fluid volume (edema). Elimination half-life can also be prolonged due to the increased Vd. Conversely, clearance may be unchanged [32], decreased [33, 34] or most frequently elevated [21, 35–37] as a result of augmented renal clearance, resulting in subtherapeutic concentrations of renally cleared antibiotics. Edematous state, commonly seen in critically ill patients, may alter the distribution of hydrophillic antibiotics (including β-lactams and aminoglycosides) and cause clinical failure of antimicrobial therapy in sepsis and/or trauma [15, 27, 38]. As a general rule, in critically ill patients Vd is 2.5-fold greater than normal, resulting in lower plasma concentrations of antibiotics. Lack of routine drug monitoring for most antibiotics makes it difficult for clinicians to distinguish between insufficient antibiotic concentrations and lack of *in vivo* microorganism susceptibility [39]. Hydrophillic antibiotics are mainly excreted unchanged by the kidney. This elimination will be limited in renal failure, which is common in the critically ill. Renal failure may occur because of trauma, multiple organ dysfunction, extensive burns, cardiogenic or hypovolaemic shock or it may be induced by use of nephrotoxic drugs [15, 27]. Those patients should receive normal antibiotic doses given less frequently, to avoid overexposure and toxic side effects [27, 39].

Hypoalbuminemia is a frequent condition in critically ill patients. It can be caused by increased albumin capillary escape rate through leaky endothelium, fluid overload or malnutrition. Hypoalbuminemia may contribute to fluid extravasation and antimicrobial dilution. On the other hand, the increase of free fraction of drug may increase Vd and clear-

ance [27]. Fortunately, for the majority of antibiotics hepatic metabolism is limited and protein binding is low enough to make no difference to their effectiveness and there is no need to alter doses [39].

Interstitial fluid (ISF) of tissues is the site of most infections and previous results showed that antibiotic concentrations in ISF are 2- to 10-fold lower than plasma concentrations, suggesting that higher plasma concentrations may be required to ensure target concentrations in ISF [40, 41]. However, the antibiotic concentrations appear to vary between different tissues, so the different plasma concentrations may be required for the same bacteria depending on tissue that is infected [38].

Antibacterial PD describes the relationship between the drug concentration and the antibacterial effect – minimum inhibitory concentration (MIC). For time-dependent antibiotics, such as β-lactams, the optimal bacterial kill is achieved by the maximum amount of time (T) over the MIC. Carbapenems require 20% and 40% of T > MIC for bacteriostatic and bactericidal activity [42]. The maximum effect is achieved when the free drug concentration above the MIC is achieved for 90–100% of the dosing interval [15]. It seems that maximum killing effects are reached at the concentration of 4 × MIC [22] to even 6 × MIC, which may represent the target concentration to suppress resistance emergence against *P. aeruginosa* [37]. Based on data obtained from the studies, imipenem is able to maintain serum concentrations higher than or equal to the MIC of 4 mg/L for almost 8 hours after a single intravenous administration. Conversely, meropenem maintains T > MIC for the whole 8-hour interval between doses only for pathogens with the MIC equal or lower than 2 mg/L. However, to obtain adequate concentrations for pathogens with higher MICs (i.e. ≥ 8 for imipenem or ≥ 4 for meropenem), it would be appropriate to increase daily doses, to use more frequent dosing or to change the administration method, from intermittent (a 30-minute infusion) bolus infusion to either a prolonged (a 3-hour/or 4-hour infusion) or continuous (a 24-hour infusion) infusion. Septic patients also may benefit from higher doses, particularly in the first 24–48 hours of the therapy [22, 37, 43]. However, even with an increased dose, the teatment failure is of particular concern for pathogens with a high MIC [37]. Our experience (unpublished data) in a study comparing the standard 30-minute bolus infusion of 1 g of meropenem with a 3-hour infusion in a 7 critically ill patients with sepsis, suggests that at a 30-minute infusion time, the 1 g dose resulted in a %T > MIC of 62.5% at a MIC of 4 mg/L, whereas a 3-hour infusion time of 1 g of meropenem resulted in a %T > MIC of 43.7% at a MIC of 4 mg/L. Against isolates with a MIC of 16 mg/L, a 30-minute infusion of 1 g of meropenem resulted in a %T > MIC of 9.5%, whereas a 3-hour infusion resulted in a %T > MIC of 12.5%. After the second dose of meropenem, about 50% of patients were underdosed with both fixed-dose antibiotic regimens.

Pharmacokinetic/pharmacodynamic concept

Although β-lactams have traditionally been administered by intermittent infusion, continuous or prolonged infusion of those antibiotics is gaining attention because of time-dependent PD and potential economic savings. Continuous infusion and intermittent infusion of β-lactams have similar clinical and microbiological outcomes [44, 45], prolonged infusion dosing strategy has resulted in favorable outcomes. Meropenem 2 g administered over 3 hours every 8 hours maintained serum concentrations and prolonged exposure at the site of infection. The prolonged infusion regimen for piperacillin-tazobactam was adopted into clinical practice in one hospital in the United States. This prolonged infusion regimen means that patients receive 3.375 g of piperacillin-tazobactam every 8 hours as a 4-hour infusion. Data suggest that the prolonged infusion regimen achieves the targeted T > MIC at a total daily dose that is less than total daily dose in standard, intermittent bolus infusion regimen (3.375 g of piperacillin-tazobactam every 6 hours). As a result, the annual reduction in drug acquisition costs was $135,750 [46]. Non-acquisition costs of antibiotic administration (time expended by medical and nursing staff, costs of disposable materials and overhead cost) should be taken into account. According to the literature, the cost-effective strategy for administering antibiotics are infusion with syringe pumps and volumetric pumps, used for prolonged or continuous infusion [47]. The dosage of antibacterial drugs in critically ill patients is not straightforward.

Data derived from two studies comparing intermittent *versus* continuos infusion of meropenem, showed that the administration of the total daily dose of meropenem (3 g) as a continuous infusion appears to increase the likelihood of achieving PD targets (40% of T > MIC) and may improve clinical outcome [48]. Administration of imipenem by continuous infusion requires additional work to reconstitute imipenem in the infusion solution due to its low solubility compared to other β-lactams. Additionally, imipenem and meropenem are the least stable β-lactams. According to the prescribing information, imipenem solutions are sufficiently stable for 4 hours at 25°C, therefore it should be reconstituted every 3 hours for treatment by continuous infusion. Although this requires additional work, it is believed that it is potentially life-saving treatment for critically ill patients [49]. The regimen for meropenem is similar. Meropenem, reconstituted in normal saline solution is stable at room temperature for approximately 6 hours [50] and drug concentration can decrease for 4% [51]. It should be administered in a cold pouch [50]. The main limitation of continuous infusion is that it ties up a line of intravascular access for the entire day, which is not practical. Critically ill patients require multiple infusions and this will require placement of other lines. Extra lines are associated with a higher probability of a central vascular catheter derived infection, which is associated with higher morbidity and cost. Prolonged infusion allows 4 hours between each 8 hours dosing interval, when other agents could be administered through the same intravenous line. The duration of infusion (3–4 hours) approximates the duration of coverage of the dosing interval with free drug in excess of the MIC that provides the maximal microbiological effect [52–54]. According to the literature, the prolonged infusion of piperacillin-tazobactam resulted in cost savings by reducing the dosing frequency from every 6 hours to every 8

hours. Based on the average wholesale price, for a the treatment period of 7 to 10 day for 50 patients in ICU in the United States, $8,765 to $12,522 were saved. The approximate 4-day decrease in ICU length of stay (LOS) resulted in cost savings of $14,000 *per* patient. In the same study, the decrease in the total days of use of meropenem in ICU was seen, because the meropenem dosing regimen did not change, just the infusion time [55]. In order to compare data, we presented our cost in US dollars. The exchange rate of 1$ was considered to be 85 dinars, year value 2012. Based on average wholesale price of piperacillin-tazobactam, for a treatment period of 7 days for the dosing frequency of every 6 hours, the direct cost would be $253 per patient. The direct cost for the treatment period of 7 days for the dosing frequency of every 8 hours would be $190 *per* patient. It seems that $63 *per* patient would be saved by reducing the dosing frequency of piperacillin-tazobactam for the treatment period of 7 days.

In a retrospective cohort study of critically ill patients with infections caused by *P. aeruginosa*, in patients with APACHE II score ≥ 17, the prolonged infusion of piperacillin-tazobactam significantly reduced 14-day mortality compared with the intermittent infusion regimen, as well as ICU LOS [52]. Meropenem administered as prolonged 3 hours infusion in dose of 1 g resulted in greater T > MICs than the dose seen after bolus infusion of the same dose of the drug. It means that the required meropenem dosage may be reduced by one half in patients infected with pathogens for which the MIC < 1μg/mL [51–53]. Another option is to decrease daily meropenem usage by one third, giving 500 mg of meropenem every 6 hours. This strategy provides similar response rates and clinical outcome and cost saving (saving of $38 *per* day for medicational acquisition and supply costs) [56]. Based on average wholesale price in our country, the use of 1000 mg of meropenem every 8 hours costs $43. The use of 500 mg of meropenem every 6 hours costs $31. If we use the same strategy and decrease daily meropenem usage by one third, the cost saving would be $12 per day.

Based on the current knowledge on the PK and PD of β-lactams, continuous or prolonged infusion regimens are recommended for treatment of less-susceptible *P.aeruginosa* and *Acinetobacter species*, due to superior achievement of target exposures in critically ill patients [27]. The delay of onset of antibacterial activity compared with intermittent administration can be circumvented by administration of an initial loading dose before continuous or prolonged infusion [54, 57].

Therapeutic drug monitoring of β-lactams in critically ill patients

Therapeutic drug monitoring (TDM) of antibiotics has traditionally been used to prevent toxicity. TDM is the standard of care for aminoglycosides and glycopeptides. This strategy has not been widely applied for β-lactams because these antibiotics have a wide therapeutic index (a ratio between the toxic dose and the therapeutic dose of drug, used as a measure of relative safety of a drug), but persistent mortality and increasing antibiotic resistance may mean that TDM of β-lactams might be one of the tools for securing favorable therapeutic outcome in critically ill patients. Measurement of drug concentrations requires the use of high-performance liquid chromatography (HPLC). According to the literature, new HPLC assay methods specifically targeting the needs of routine TDM application have been developed, thus enabling simultaneous determination of β-lactams [58–61]. However, HPLC is a relatively slow, costly technique that requires extensive sample preparation and clean-up process and thus not suitable for urgent assay needs. On the other hand, immunochemical assays techniques, which are used for TDM of aminoglycosides and vancomycin, use the cheaper and easy-to-use instrumentations. To date, no technique allows simple and rapid determination of unbound β-lactam plasma concentration, which is ideally required for TDM [37].

TDM of β-lactams in an ICU may be appropriate because underdosing is associated with worse clinical outcome; PK changes are frequently large and unpredictible, even when creatinin clearance is used to guide dosage adjustment; suboptimal drug exposures may be important in the development of antimicrobial resistance.

Conclusion

Determining the optimum dosing strategy for β-lactams in critically ill patients is very important. Data from various pharmacokinetic/pharmacodynamic analysis suggest that a clinical difference between continuous/prolonged and intermittent infusion of those antibiotics still exists. Based on literature data, it seems reasonable to use the continuous or prolonged infusion regimen of β-lactams, because improved outcome can be achieved by prolonging the T > MIC. However, until the clinical benefits are clearly confirmed by well-designed large randomized controlled trials, β-lactams are not recommended for routine use as prolonged or continuous infusion. Pharmacoeconomic analysis of these regimens should also be included in future trials.

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