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Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: A narrative and systematic review☆

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ABSTRACT

Purpose: The purpose of this study is to review the rationale of prolonged (ie, extended or continuous) infusion of piperacillin/tazobactam (PIP/TAZ) in critically ill patients and to perform a systematic review that compare the effectiveness of prolonged infusion with intermittent bolus of PIP/TAZ.
Materials and methods: A search of Medline, Web of Science, Embase, and Cochrane databases was conducted up to April 2014. For systematic review, studies comparing the effectiveness of prolonged and bolus administration of PIP/TAZ were included. The level of evidence is determined using best-evidence synthesis, which consisted of 5 possible levels of evidence: strong, moderate, limited, conflicting, or no evidence.
Results: The pharmacokinetic/pharmacodynamic studies that account for an eventual benefit of prolonged PIP/TAZ infusion were reviewed. In the systematic review, 1 randomized controlled trial was identified that showed higher "cure" in the prolonged than in the intermittent infusion group, yet the chosen clinical outcome in this study, decline in mean Acute Physiology and Chronic Health Evaluation II score is controversial. Of 6 retrospective cohort studies, 4 showed either less mortality, a higher clinical cure rate, or shorter length of hospital stay with prolonged PIP/TAZ treatment. The level of evidence supporting a better clinical outcome with prolonged infusion of PIP/TAZ is moderate.
Conclusion: Pharmacokinetic/pharmacodynamic studies provide a robust rationale to prefer prolonged above intermittent infusion of PIP/TAZ. However, although some studies suggest a better outcome in critically ill patients receiving prolonged infusion, the level of evidence is moderate.

1. Introduction

Piperacillin/tazobactam (PIP/TAZ) is a broad spectrum combination antibiotic commonly used to treat severe infections in the intensive care unit (ICU) [1]. It consists of 2 active components: piperacillin with high-antimicrobial activity and tazobactam, a β-lactamase inhibitor with limited antimicrobial activity [2]. Tazobactam inactivates β-lactamase enzymes produced by bacteria [2], thereby restoring their susceptibility [3]. Despite this interesting microbiological profile, optimization of pharmacokinetic/pharmacodynamic (PK/PD) behavior of PIP/TAZ remains needed to improve treatment outcome and to prevent selection and spread of resistant strains [4-7]. Pharmacokinetics provides information about the movement of a drug from its administration site to the site of action and its elimination from the body. Pharmacodynamics for a given antibiotic refers to its ability to kill or inhibit the growth of microorganisms. A key PD feature of an antimicrobial is the minimum inhibitory concentration (MIC). *Minimum inhibitory concentration* is the term that is used to express the lowest concentration of an antibiotic that inhibits bacterial growth. Pharmacokinetic/pharmacodynamic study combines pharmacokinetic and pharmacodynamics features to predict the probability of successful antibiotic treatment [8]. From a PK/PD perspective, various antibiotic classes show different bacterial kill characteristics. Preclinical studies have defined PIP/TAZ as time-dependent antibiotic; the time during which the free (unbound) antibiotic concentration is maintained above the MIC ($fT_{>MIC}$), and not the magnitude of its concentration, is the determining factor for bacterial killing [9,10].

Piperacillin/tazobactam has a short half-life (between 0.8 and 1.1 hour) [11] and is given intravenously because of its poor oral absorption [2], generally in bolus dose (ie, infused over 20-60 minutes every 6 or 8 hours) [6,12]. Arguably, giving PIP/TAZ PD features to produce sustained/PD features to produce sustained $fT_{>MIC}$ [13]. For this reason, continuous administration has been proposed as a valuable alternative. However, ICU physicians often argue against this strategy because it requires a dedicated venous access and may cause unwarranted incompatibility with other intravenous therapy. Another proposed method is extended administration, which can be defined as an infusion time beyond 1 hour [14]. Several reviews have

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compared continuous with intermittent administration of β-lactam antibiotics [15-18], but none has specifically focused on PIP/TAZ in an ICU setting. Critically ill patients in particular might benefit from prolonged PIP/TAZ infusion [19], for the reasons that will be explained below. We also noticed that the published reviews often did not discuss other types of prolonged infusion than continuous infusion, and they discussed only PK/PD characteristics [16] or only clinical outcome [15]. Furthermore, new studies have been published since the last review [20-22]. Therefore, a systematic review with updated information on PK/PD and clinical outcome of PIP/TAZ use in ICU setting is needed.

The present article has 2 aims. First, to assess the rationale of prolonged (ie, extended or continuous) infusion of PIP/TAZ in critically ill patients. Second, to perform a qualitative systematic review comparing the effectiveness of prolonged vs intermittent bolus of PIP/TAZ.

2. Rationale of prolonged infusion of PIP/TAZ in critically ill patients

Intensive care unit patients differ from other hospitalized patients in terms of pathophysiology and disease severity. Both factors will affect drug metabolism and PK/PD behavior. For example, the microvascular endothelium becomes highly permeable during sepsis [23]. This will augment the distribution volume (a theoretical volume that relates the plasma concentration of a drug to the administered dose) of hydrophilic drugs such as PIP/TAZ [19]. Volume resuscitation during the early stage of severe sepsis also highly increases cardiac output, thereby enhancing renal and hepatic blood flow [24]. This will significantly affect PIP/TAZ metabolism and excretion rate because piperacillin is mainly (50%-60%) excreted by the kidney and partly in bile [2]. Increased distribution volume and clearance will finally result in lower plasma piperacillin concentrations. This is confirmed by studies showing maximum plasma piperacillin concentrations of 380 mg/L in healthy volunteers [10] and 231 mg/L [11] in ICU patients after intermittent infusion of 4 g piperacillin [10,11].

Augmented renal clearance (ie, elevated renal elimination resulting in subtherapeutic plasma concentrations) of antibiotics is increasingly reported in critically ill patients [25,26]. This phenomenon is probably related to the innate immune response to infection and inflammation (with its associated systemic and hemodynamic consequences) but also to fluid loading and use of vasoactive medications. As a result, cardiac output and renal blood flow increase, which subsequently lead to enhanced glomerular filtration. Increased filtration induces substantial drug elimination and causes subtherapeutic antibiotic plasma levels [25]. Therefore, alternative antibiotic dosing regimens (ie, other than "traditional" intermittent bolus infusion) must be considered when augmented renal clearance is present to offer better treatment options and to reduce the risk of resistance development.

As mentioned above, the $fT_{>MIC}$ is an important determinant of bacterial killing when β-lactam antibiotics are used. Animal studies showed that $T_{>MIC}$ between 40% and 70% of the dosing interval is required [11]. Rafati et al [27] studied $T_{>MIC}$ in 40 septic critically ill patients. The $T_{>MIC}$ (many studies mentioned $T_{>MIC}$ instead of $fT_{>MIC}$ which does not specifically mention the measurement of free antibiotic concentration) of continuous infusion of PIP/TAZ (2 g/0.25 g loading dose over 30 minutes followed by 8 g/1 g daily) was higher than the $T_{>MIC}$ after intermittent bolus of PIP/TAZ (3 g/0.375 over 30 minutes every 6 hours): 100% vs 62% and 65% vs 39% for an MIC of 16 mg/L and 32 mg/L, respectively. Noteworthy, these MICs values are high. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) considers *Pseudomonas aeruginosa* with an MIC higher as 16 mg/L as resistant (EUCAST breakpoint table, version 3.1). Dulhunty et al [28] showed that patients under continuous infusion of PIP/TAZ more often reached plasma antibiotic concentrations above the MIC than patients receiving intermittent bolus (9 [75%] of 12 vs 4 [36%] of 11, respectively). In this study, the 24-hour dose was chosen at the clinician's discretion. Two studies using a Monte Carlo simulation to calculate probability of target attainment (ie, the probability that a specific value of a PD index [eg, 50% $fT_{>MIC}$] is achieved at a certain MIC) also confirmed the benefit of prolonged infusion [29,30]. Using MIC distributions from Canadian ICU surveillance data, Zelenitsky et al [29] showed that the cumulative target attainment, determined by integrating each probability of target attainment with the corresponding pathogen and MIC distributions from Canadian ICU surveillance data of 50% $fT_{>MIC}$ in extended infusion (3-hour infusion of 3 g/0.375 g PIP/TAZ every 6 hours) was higher than when an intermittent bolus (30-minute infusion of an equivalent PIP/TAZ dose at similar frequency) was provided (0.84 vs 0.79) . This difference became even more significant in favor of extended infusion at the 100% $fT_{>MIC}$ (0.63 vs 0.36). For an MIC of 1 mg/L, Roberts et al [30] demonstrated a 50% $fT_{>MIC}$ for continuous (8 g/1 g over 24 hours), extended (4 g/0.5 g every 8 hours), and intermittent bolus (4 g/0.5 g every 8 hours) infusion of PIP/TAZ of respectively 0.55, 0.43, and 0.26. Several retrospective clinical studies have demonstrated that larger drug exposures are required, with β-lactam concentrations up to 4 times the MIC for the entire dosing ($T_{>4\times MIC}$) [31,32]. In critically ill patients with pathophysiology changes, this high PK/PD target can be obtained by using continuous infusion. Again, the literature shows that this purpose can be obtained with more frequent dosing or by extended or continuous infusions [10,33]. Duszynska et al [32,34] elegantly proved the relationship between the percentages of $T_{>4\times MIC}$ and improved clinical outcome. In 16 patients with ventilator-associated pneumonia (VAP), these investigators showed that continuous infusion of 10.0/1.25 g PIP/TAZ produced adequate therapeutic drug concentrations (defined as $T_{>4\times MIC}$) on the first day of treatment for 71% of the isolated pathogens. Clinical cure was achieved in 90% of the patients with adequate drug concentrations vs 50% in patients with insufficient levels [32,34].

Few studies have investigated tissue penetration of PIP/TAZ. The results of these studies suggest that bolus infusion can achieve tissue concentration of PIP/TAZ above the MIC breakpoint according to EUCAST or Clinical and Laboratory Standards Institute, but the concentration might be suboptimal. Joukhadar et al [35] showed that mean piperacillin concentrations in subcutaneous adipose tissue never exceeded 11 mg/L in septic shock patients who were given 4 g/0.5 g PIP/TAZ. This tissue concentration is just higher than one-step dilution of MIC 16 mg/L. Another group investigated concurrent plasma and subcutaneous tissue concentrations in critically ill septic patients after receiving continuous vs intermittent bolus of PIP/TAZ. They concluded that continuous infusion more successfully achieved tissue PD targets and enabled to maintain higher trough concentrations compared with standard bolus dosing [36]. In critically ill patients with severe bacterial pneumonia treated with 4 g/0.5 g PIP/TAZ every 8 hours, Boselli et al [37] found PIP/TAZ epithelial lining fluid concentration (SD) of 13.6 (9.4) mg/L/2.1 (1.1) mg/L. They concluded that the given PIP/TAZ regimen might provide insufficient concentrations into lung tissue to exceed the MIC of many causative pathogens [37].

3. Systematic review on comparing clinical outcome of prolonged vs intermittent bolus infusion of PIP/TAZ

3.1. Literature search and data extraction

Together with medical librarians, we searched Medline, Science Citation Index through Web of Science, Embase, and Cochrane up to April 2014. Search terms were "piperacillin" or "piperacillin/tazobactam" and "intensive care unit" or "critically ill" or "critical illness" or "critical care" or "intensive care unit" and "pharmacokinetics" or "pharmacodynamics" or "extended infusion" or "continuous infusion." Only English language articles were reviewed. We excluded data from critically ill children and from patients undergoing renal replacement therapy. Complete search strategies are shown in Appendix I.

Two reviewers read the title and the abstracts of all retrieved references for obvious exclusions. They subsequently read the full text of remaining references. References of included studies were screened