Therapeutic Drug Monitoring of Beta-Lactam Antibiotics

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Here describes various aspects of beta-lactams use in the critical care, focusing on clinical antibiotic stewardship in the ICU. Pharmacokinetics / pharmacodynamics (PK/PD) characteristics of beta-lactams are described and main factors of PK/PD variability in critically ill patients. Toxicity of beta-lactams, a frequently overlooked issue, is outlined. Analytical methods used in therapeutic drug monitoring (TDM) of beta-lactams are discussed. The evidence supporting antibiotic guidance based on therapeutic drug monitoring (TDM) in critically ill patients is analysed.

Keywords: beta-lactam antibiotics ; pharmacokinetics–pharmacodynamics ; critically ill

1. Beta-Lactam Pharmacokinetics/Pharmacodynamics (PK/PD) General Characteristics

Achieving the adequate concentration of any antibiotic at the site of infection and preventing bacterial resistance is crucial for good clinical practice. The knowledge of the pharmacodynamics and pharmacokinetics of any antibiotic is essential for formulating an optimal dosing regimen. Different groups of antibiotics demonstrate various PK/PD properties. The clinical effectiveness of beta-lactams is based on the time that their unbound fraction spent above the minimum inhibitory concentrations (MICs) of the susceptible microorganisms [1][2]. This phenomenon is called time-dependent killing [3]. Beta-lactam antibiotics are small hydrophilic molecules with a low volume of distribution (V_d) characterized by tissue distribution limited to the extracellular space, i.e., plasma and interstitial compartment. This results in limited penetration across biological barriers. Binding to plasma proteins is significant in cephalosporins except for cefotaxime, ceftaroline, ceftolozane and cefepime. Ertapenem, flucloxacillin and oxacillin also display high binding to plasma proteins (>30–50%), while the free fraction of the remaining beta-lactams exceeds 80%. Apart from ceftazidime, ceftriaxone, ceftaroline and ceftolozane, the elimination half-life of beta-lactams is less than 2 h. The PK/PD characteristics of beta-lactam antibiotics are summarized in Table 1. Since most of these antibiotics are excreted primarily via glomerular filtration in kidneys, renal functions are critical factors affecting antimicrobial concentration [4].

2. Biochemical Assays for TDM of Beta-Lactam Antibiotics

Routine antibiotic analysis in clinical laboratories is usually limited to aminoglycosides and vancomycin to prevent their nephro- and oto- toxic effects [5]. These antibiotics are analyzed by various immunoassays, such as the kinetic interaction of microparticles in solution (KIMS), cloned enzyme donor immunoassay (CEDIA), and particle-enhanced turbidimetric inhibitor immunoassay (PETINIA), to name a few [6]. These methods are performed on clinical chemistry automated analyzers—standard equipment in all clinical laboratories developed and maintained by in vitro diagnostics (IVD) companies. The main advantage of immunoassays is their fast implementation in the laboratory. Since reagents come in ready-to-use packs, laboratory staff require only short training and automated analyzers enable the high throughput of samples, as all tests are performed in parallel. From a clinician’s point of view, the main advantage is the fast turnaround time (TAT). However, due to high initial costs, only a limited portfolio of antibiotics is currently available for TDM immunoassay analysis [7]. Due to the variability of companies with a portfolio of analyzers based on a similar analysis principle, these tests can be performed in most current clinical laboratories. On the other hand, immunoassays provide a greater chance of possible interferences and cross-reactions, resulting in false results.

An increased range of antibiotics for TDM may be attained by utilizing chromatographic methods, predominantly high-performance liquid chromatography (HPLC) coupled with ultraviolet (UV) [8] or mass spectrometry (MS) [9] detectors. Several companies have developed methods of ready-to-use kits for the quantitative analysis of several antibiotics, including beta-lactams, in plasma. However, since instrumentation in different laboratories vary, the method transfer is

more complicated and time-consuming than with the previously described immunoassay methods [10]. The low throughput of the analyzers is another disadvantage of the chromatographic methods. Patient samples, as well as internal controls and calibrators, must first undergo a timely and complicated extraction process. The analysis is then performed in tandem. This leads to long TATs, which diminish the effectiveness of the TDM process. The advantages are the possibility of simultaneous analysis of several analytes [11] and robust results with high specificity and sensitivity. Another advantage of chromatographic methods is the ability to develop methods on-site (in-house), so the laboratories can provide a larger portfolio of analytes. However, in-house method development and method validation is very time consuming and requires skilled analytical personnel [7][12].

Quite recently, the analysis of ceftazidime and piperacillin via immunoassay on a tabletop analyzer was introduced, ensuring short TAT and allowing a point-of-care (POC) setting. Another feasible approach may be the automation of the HPLC methods coupled with a mass analyzer [13].

3. Microbiological Susceptibility Testing

The determination of MIC has gained a reputation as the golden standard of antibiotic stewardship over the past decades [14]. When trying to achieve a defined plasmatic level of an antibiotic based on minimal inhibitory concentration testing, the clinician must understand the potential drawbacks of this approach. MIC is provided by the in vitro testing of the inhibition of bacterial growth in standardized inoculum on standardized media using a defined assay. It utilizes two-fold dilution above and under the antibiotic concentration of 1 mg/L, so the resulting concentration is typically expressed as one value from the interval (0.002, 0.004, 0.032… 256, 512) mg/L [15]. The first shortcoming arises from the time needed for culture and testing. As it reaches at least 48 h in most settings, it leaves questions regarding the adequacy of the treatment for quite a significant time [16]. The second drawback of MIC testing stems from the variability of the results themselves. Bacterial strains without any acquired resistance, so-called wild type (WT) bacteria, demonstrate distribution around three to five two-fold concentrations. The highest WT concentration within the limits of natural distribution is defined as the epidemiological cut-off (ECOFF). These data are regularly updated by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and are available online [17]. Another source of MIC variation is caused by assay differences. It has been shown that if MICs are determined several times in more than one laboratory, over half of the variability is due to strain-to-strain variation and inter-laboratory differences, with the remainder being attributed to the assays themselves [18].

The PK/PD objective of beta-lactams is expressed as the percentage of time, during which the free antimicrobial's fraction in plasma exceeds a certain concentration (% fT > concentration). Hypothetically, the target concentration should be equal to the MIC of the treated pathogen. Considering MIC variability, the use of one single MIC value obtained by MIC determination for achieving 50–100% fT > MIC is rather inappropriate and higher PK/PD targets seem necessary. To prevent antibiotic underdosing regarding MIC variability, an individualized approach was suggested. If MIC falls into a low-level resistance area, indicating that the strain is within the WT distribution range, the upper ECOFF value should be taken as a target. If the MIC is above the upper ECOFF value but still below the clinical resistance breakpoint, the PK/PD target should be set as MIC + two-fold dilution, meaning four times the MIC value for the 100% of the dosing interval (fT ≥ 4 × MIC = 100%). If the MIC value that is clearly above the clinical resistance breakpoint, switching to a different antibiotic is a clear option [19].

Assays using a modified MIC approach were developed to assess serum antibiotic levels. The main advantage comes with lower costs and technological requirements. From their introduction in voriconazole [20], microbiological methods have proven effective in determining cefotaxime, meropenem and piperacillin, resulting in strong correlations with values obtained by HPLC [21].

4. Beta-Lactam Toxicity

Clinically relevant beta-lactam toxicity comprises effects on the central nervous system, hepatotoxicity, myelosuppression, nephrotoxicity and *Clostridoides difficile* infection (CDI) [22]. Over the past few decades, the neurotoxic effects of beta-lactams have become more familiar among clinicians. The reported clinical manifestation ranges from electroencephalographic changes, the altered quantitative level of consciousness, confusion, hallucinations, movement disorders (asterixis, dyskinesis), myoclonus and, most importantly, seizures or even status epilepticus [2][23]. The overall incidence of beta-lactam-related neurotoxicity remains debatable. In patients treated with cefepime, piperacillin/tazobactam or meropenem, up to 15% experienced signs of neurotoxicity [23]. Nevertheless, in a recent retrospective cohort study, the overall incidence was found to be between 2.1% and 2.6% [24]. The greatest potential for inducing seizures was described in cefazolin and cefepime, followed by penicillin G and imipenem [22]. As beta-lactams

cross the blood–brain barrier, a direct relationship between high plasmatic concentrations and neurotoxicity was found. Renal dysfunction with an unpredictable increase in plasmatic and tissue concentrations of beta-lactams presents a major risk factor, with a history of neurological disorders also being a predisposing factor [22][25][26]. Potential toxicity mediated by concentrations (when applied by discontinuous infusions) and steady-state (in case of continuous infusions) concentrations in plasma were identified for flucloxacillin, amoxicillin, ceftazidime, piperacillin/tazobactam, cefepime, imipenem and meropenem [2][23][27][28][29].

The nephrotoxic effects of beta-lactams remain underrated but still debated. The risk of nephrotoxicity is even higher when combined with certain known nephrotoxic drugs, e.g., vancomycin, especially in patients with premorbid kidney disease or older age [22][30]. Although the reported incidence is highly variable [22] and direct causality can be found only rarely, the deterioration of kidney functions puts critically ill patients at a greater risk of death [31]. Despite epidemiological data showing an association of AKI with beta-lactam administration, direct causality can be found only rarely. A possible increase in AKI related to the combination of antibiotics, for example, the most frequently used piperacillin and vancomycin, is not based on evidence of causality [32]. Surprisingly, data suggesting the protective role of a combination of piperacillin and vancomycin exist [33][34]. Additionally, these conflicting data regarding nephrotoxicity are based on serum creatinine increase [35]. The proximal tubular secretion of creatinine could be reduced by several antibiotics, including piperacillin or vancomycin. They bind with higher affinity to renal transporters mediating creatinine secretion and, consequently, serum creatinine levels increase. Thus, the association with AKI defined by creatinine levels should be called pseudotoxicity, rather than defined as a real toxic effect [32]. As already mentioned, using a single creatinine level in estimating GFR in a critically ill patient is not appropriate, and other approaches, such as measuring cystatin levels or four-hour creatinine clearance, should be prioritized [36][37].

Acute interstitial nephritis is the usual underlying mechanism with non-IgE mediated hypersensitivity reaction and T-lymphocyte involvement [22][38]. When clinical suspicion is supported by skin rash and microscopic hematuria with proteinuria, corticosteroids represent a therapeutic option [39].

Myelosuppression with severe neutropenia is a rare but potentially fatal complication of beta-lactam exposure, usually resolving after discontinuation of the treatment [40]. Cross-reactions after the institution of different beta-lactam antibiotics have also been described.

As the toxic effects of beta-lactams are directly related to their plasmatic concentration, the upper limit of plasmatic concentration 8 × MIC should not be exceeded [1][2].

5. PK/PD Targets for Beta-Lactam Antibiotics

As mentioned earlier, the PK/PD target directly connected to the bactericidal effect of beta-lactams is expressed as the percentage of time during which the free antimicrobial's fraction in plasma spends above a certain level (% fT > concentration). As the post-antibiotic effect of beta-lactams is variable, the peak plasma concentration has no significant benefits [4][41][42] and is not standardly accounted for. The required concentration of a particular beta-lactam antibiotic is dependent upon the MIC of the causative pathogen. Based on experimental data, the PK/PD index associated with optimal beta-lactam activity was defined as fT > MIC at 50–70% for most infections [1]. However, maintaining the concentration above MIC 100% of the time was shown to be associated with better outcomes in critically ill patients [43][44]. When taking into account microbiological testing variability and inconsistent penetration into infected tissues, even higher PK/PD targets are preferable. To deal with all sources of individual variability, a concentration four times higher than the MIC for 100% of the dosing interval should be achieved to optimize clinical outcomes and, at least, to prevent the selection of resistant bacterial subpopulations [2][45]. Whether this approach helps improve clinical outcomes is not yet proven; moreover, the DALI study was not able to show the utility of the PK/PD concepts in the clinical setting of this trial [43]. Considering the threshold for toxicity, the target concentration of beta-lactam antibiotics should be between four- and eight-times above MIC for 100% of the time (fT ≥ 4–8 × MIC = 100%) [2].

6. Modes of Applications of Beta-Lactam Antibiotics

For beta-lactams, as typical time-dependent killing antibiotics, optimal PK/PD targets of beta-lactams are achieved by keeping the plasmatic concentration within certain concentration limits without major fluctuations. Based on population pharmacokinetic studies, extended-length (usually ≥ 3 h) or continuous infusions following a loading dose provide better attainment of PK targets than standard infusions [46][47][48]. The clinical benefit was proven in patients with severe sepsis [49], and although this finding may not be consistent [50], results of meta-analyses suggest better outcomes in septic patients treated with this strategy [51][52][53]. These outcomes were most prominent in critically ill or immunocompromised

patients with infections caused by non-fermenting Gram-negative bacteria, especially *Pseudomonas aeruginosa* [54][55]. Prolonged infusion resulted in improved outcomes in patients with lower respiratory tract infections [51][56]. The administration of beta-lactams in prolonged or continuous infusions has also been recommended in the latest Surviving Sepsis Campaign guidelines [57].

The chemical stability of beta-lactam infusions lasting more than several hours has been questioned. This becomes an issue with imipenem (2 h), meropenem and ertapenem (6 h). Other beta-lactams remain stable after reconstitution in a 0.9% NaCl solution for more than 8–12 h, enabling their safe use in form of a continuous infusion with several changes of a new antibiotic solution per day [58][59].

When applying a beta-lactam antibiotic in the form of a continuous or prolonged infusion, the application of a loading dose is crucial [2][54]. The optimum initial dose for each antibiotic is calculated primarily by its V_d and should not be modified according to the degree of organ dysfunction. The administration of a loading dose identical to the dose used in intermittent application seems to be a reasonable approach.

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