Editorial
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# Prolonged or Continuous Infusion of IV Antibiotics as Initial Treatment Strategy

Hyuck Lee

Division of Infectious Diseases, Department of Internal Medicine, Dong-A University Hospital, Busan, Korea

Parenteral administration of β-lactam antibiotics by intermittent intravenous infusion or intramuscular injection has been considered the optimal dosing regimen. The exposure of staphylococci, streptococci, and enterococci to different β-lactams shows a post-antibiotic effect (PAE) that lasts for several hours duration [1]. This phenomenon of persistent suppression of Gram-positive cocci supported the institution of intermittent dosing regimens for β-lactam antibiotics. This strategic use of these antibiotics appeared to exhibit a reasonable level of success in clinical practice. However, the increasing number of emerging cases of drug resistance, the rising incidence of Gram-negative bacillary infections, and the lack of new antibiotics suggest that it may be appropriate to consider the development of more effective means of optimizing the use of old and new antibiotics to treat infections. Considerable progress has been made over the past two decades in elucidating the exposure–response relationships of antimicrobials, particularly the pharmacokinetic (PK) and pharmacodynamic (PD) principles. New strategies for improving antimicrobial therapy should have two primary objectives, which are to improve the patient outcome and decrease the health care costs. In this regard, the continuous infusion of β-lactam antibiotics has been investigated and proposed as a new dosage regimen to achieve the most benefit with the least amount of drug [2].

The prolonged or continuous infusion of antimicrobial agents has been suggested as a means of optimizing therapy for infectious diseases. The opponents of this approach claim there is a lack of clinical evidence and the need for extensive resources to support this methodology. On the other hand, the proponents hold the position that the prolonged infusion of antimicrobials could contribute to combating the potential misuse of time-dependent antimicrobials, which has been driven by several misunderstandings. These include the fact that a laboratory-reported "S" (for "susceptible") indicates that the agent will be effective while all "S" designations are equal. Furthermore, the manufacturer-recommended doses are always higher than required. If treatment failure occurs, it must be due to factors other than the antimicrobial agent while resistance is "inevitable," and discovering new agents is the only solution.

The prolonged infusion of time-dependent antibiotics maximizes the achievement of relevant therapeutic concentrations over time (*i.e.* PK) and enables the maximum action of the drug (*i.e.* PD). The PK/PD of antimicrobials are the foundation

**Corresponding Author :** Hyuck Lee, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Dong-A University Hospital, 26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea
Tel: +82-51-240-5047, Fax: +82-51-243-5047
E-mail: hleeid@dau.ac.kr

of drug dose establishment, which is aimed at optimizing the clinical outcomes [3]. PK/PD evaluations are essential in the study of new agents to determine the best dosing regimens and establish microbiological breakpoints for susceptibility [4, 5]. For existing antimicrobials, the PK/PD are used to investigate the adequacy of traditional dosing regarding clinical efficacy and the emergence of resistance [6, 7] . Once established in clinical trials, the PK/PD principles provide valuable information for further exploration.

Standard recommended doses are largely based on the "average" or "typical" patient, with little guidance for dose individualization. Therefore, standard recommended doses cannot meet the needs of all patients. The same PK/PD principles that are used to generate regimens for the "average" patient can currently be used to determine adequate dosages for those at high risk of antimicrobial failure. These patients may include people with significantly altered PK (*e.g.* owing to obesity, critical illness, or burns), immunosuppression (*e.g.* induced by diabetes mellitus or neutropenia), or infections involving less susceptible pathogens (*e.g. Pseudomonas aeruginosa*). In these situations, the prolonged infusions of time-dependent antimicrobials over 2 to 4 h could achieve PK/PD targets that are not attainable by using standard administration regimens. For example, the advantages of prolonged infusion have become evident for piperacillin–tazobactam, an extended-spectrum penicillin widely used in the treatment of serious infections such as intra-abdominal sepsis and nosocomial pneumonia.

The Monte Carlo simulation is a robust research tool that is extensively used in engineering, computer sciences, finance, and more recently, the biomedical sciences. In the area of antimicrobial PK/PD, which has numerous confounding variables, the Monte Carlo simulation can be used to evaluate dosing regimens in a large number of simulated patients based on specific demographics, antimicrobial PK/PD, and pathogen susceptibilities. Therefore, instead of defaulting to the "average" patients or worst-case scenarios, practitioners can now use the results of the Monte Carlo simulations that are relevant to the patient populations of interest. The use of the Monte Carlo simulation led to the discovery that the standard piperacillin–tazobactam dosing would achieve the therapeutic target to a lower degree than simply prolonging the infusion, which would enable the threshold to be reached at a more targeted level. The clinical benefits of the prolonged infusion of piperacillin-tazobactam have been demonstrated [8]. In a study of patients receiving piperacillin–tazobactam for infections with susceptible *P. aeruginosa*, the mortality rates were considerably lower in those who received prolonged infusions than in those who received standard intermittent doses.

There have been longstanding concerns about the adequacy of piperacillin–tazobactam for treating pseudomonal infections. In fact, for nosocomial pneumonia, the current product monograph recommends that piperacillin–tazobactam be administered at a dosage of 4.5 g every 6 h (q6h) in combination with an aminoglycoside [9]. The rationale for such concern and aggressive therapy are consistent with the argument suggesting poor target attainment with standard recommended doses. However, the PK/PD advantages of increasing the dose only are minimal compared with those of other strategies such as prolonged infusion.

Several disadvantages have been identified with the use of continuous infusion. 1) A delay in drug tissue equilibration occurs because of the lag time for the serum concentration to reach a steady state. However, the administration of a loading-dose prior to the continuous infusion would ensure the rapid onset of antibacterial activity [2]. 2) There is decreased patient mobility when intramuscular injections or intravenous catheters with a heparin lock are administered.

There are a limited number of published studies comparing the rate or extent of tissue penetration following the continuous infusion and intermittent injection of β-lactams. Most of the current studies were performed in animal models and, therefore, require extrapolation to humans. In general, the amount of drug delivered to the interstitial fluid, as measured by the area under the concentration–time curve (AUC), was greater with intermittent injections or a single bolus injection than it was with constant infusion. However, the difference between these regimens was reduced considerably when the animals were administered an initial bolus dose prior to the continuous infusion [2].

There are also a few issues related to the use of extended infusions that should be considered. Some β-lactams may not be stable for long enough to allow extended infusion. Furthermore, additional lines may be needed to prevent incompatibilities with other drugs. However, any concerns about the logistical barriers and the resources needed to administer prolonged infusions of antimicrobials are outweighed by the potential life-saving benefits of individualized therapy.

Presently, the clinical data do not support the widespread use of continuous or prolonged infusions of β-lactams, and it is unlikely to have a significant impact on meeting the challenges of increasing Gram-negative resistance and, at best, it will allow the treatment of borderline or low-level resistance.

Treatment guidelines that are current and state of the art could be instituted for either prolonged or continuous infusion of β-lactams for which a reasonable database exists. Some fine points are emerging and accumulating. Some investigators have elected to start with an initial ("loading") dose while some have not. Further, the interval between an "initial" dose and the first prolonged infusion or the start of the continuous infusion is currently a guesstimate, at best.

Therefore, the present challenge for clinicians is to determine the specific patient groups as well as the healthcare settings that are most likely to be benefitial [10]. In addition, the clinicians need to decide the clinical trials that have exhibited compelling outcomes in severe sepsis and patients with multiple comorbidities and, therefore, would be suitable for adoption into practice in the near future.

## ORCID

Hyuck Lee *http://orcid.org/0000-0002-4115-0748*

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