Prolonged β-Lactam Infusion for Gram-negative Infections

Pranita D. Tamma, MD, Alice M. Jenh, PharmD, and Aaron M. Milstone, MD, MHS

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The emergence of multidrug-resistant organisms coupled with an alarming scarcity of new antibiotic classes in the pipelines of the pharmaceutical industry has forced the healthcare community to optimize the therapeutic potential of currently available antibiotics.

The primary determinant of β-lactam efficacy is the duration of time in which the nonprotein-bound drug concentration (IT) exceeds the minimum inhibitory concentration (MIC) of the organism (IT > MIC).1 With intermittent dosing, β-lactams attain a high peak concentration, but short half-lives can lead to precipitous drops in their serum drug levels. Optimizing IT > MIC is particularly difficult for organisms with elevated MICs. Prolonging the infusion time provides more consistent serum levels and maximizes IT > MIC (Fig. 1).2–5

Prolonging the infusion of β-lactams consists of either extended infusion or continuous infusion. Extended infusions are defined as intermittent infusions lasting ≥3 hours, whereas continuous infusion involves infusion over a 24-hour period at a fixed rate.6 To date, all clinical outcome studies of prolonged β-lactam infusions for Gram-negative infections have been conducted in adults. In this review, we outline the available clinical data on prolonged β-lactam administration and propose infusion strategies that could be considered in pediatric patients.

PIPERACILLIN-TAZOBACTAM

Three prospective and 3 retrospective studies evaluating clinical outcomes of Gram-negative sepsis in recipients of prolonged infusion piperacillin (PIP) or piperacillin-tazobactam (PIP-TAZ) have been conducted.7–12 A randomized controlled trial (RCT) demonstrated that continuous infusion PIP reduced the severity of illness of critically ill adults more rapidly than intermittent infusions.8 Results from a second RCT did not reveal a clinical benefit.9 A prospective, controlled trial of continuous infusion PIP-TAZ revealed a trend toward greater clinical success in the continuous infusion group when compared with intermittent infusion recipients.10

A significantly lower 14-day mortality rate and shorter hospital length of stay in patients receiving extended infusion, compared with intermittent infusion PIP-TAZ for Pseudomonas aeruginosa sepsis was demonstrated in a retrospective, cohort study.7 Results from another retrospective cohort study showed increased clinical cure by continuous compared with intermittent PIP-TAZ infusion in adults with ventilator-associated pneumonia (VAP) caused by Gram-negative organisms with MICs ≥8 μg/mL.11 A third retrospective cohort study, however, failed to demonstrate improved clinical outcomes with extended infusion PIP-TAZ.12

The above studies excluded patients with severe renal dysfunction and generally consisted of patients infected with organisms with low MICs (≤8 μg/mL). Drug-related adverse effects were mild and reported in similar numbers in both treatment arms and no emergence of resistance was reported.7–12 Although the data on prolonged infusion PIP-TAZ are generally favorable, results are inconsistent. Stability data regarding PIP-TAZ indicate it is suitable for continuous infusion over 24-hour at room temperature.13

CEFTAZIDIME

Four RCTs have been undertaken to evaluate clinical outcomes of continuous versus intermittent infusion ceftazidime (CFZ) for Gram-negative infections.2–5 These trials did not demonstrate a clinical benefit of continuous CFZ infusion; however, they all had small sample sizes (n ≤ 35). A retrospective cohort study of patients with VAP demonstrated that continuous CFZ infusion was associated with greater clinical cure rates than intermittent infusion.14 There were no significant differences in adverse effects between infusion strategies, and development of resistance was not observed.2–5,14 Clinical data evaluating the use of extended infusion cephalosporins are not available. As CFZ is less stable for continuous infusion at temperatures >25°C, mechanisms must be in place to ensure the medication remains ≥25°C for the entire 24 hours of infusion, or infusions should be changed at least every 8 hours.13

CEFEPI MEME

A single RCT including patients with Gram-negative pneumonia or bacteremia comparing continuous with intermittent infusion of ceftazime (CEF) did not find any differences with respect to clinical cure rates.15 Similar to CFZ, CEF is less stable at temperatures >25°C
and new solutions should be administered at least every 12 hours.13

**MEROPENEM**

To date, meropenem (MER) infusion strategies have not been compared in RCTs; however, a retrospective cohort study in VAP patients demonstrated significantly improved clinical cure rates with continuous versus intermittent infusion of MER.16 For carbapenems, the fT > MIC required for bactericidal activity is lower than other β-lactams (40%, 50%, and 60%–70%, for carbapenems, penicillins, and cephalosporins, respectively).1 Additional- tionally, carbapenems are even more unstable at room temperature compared with cephalo- sporins. Pharmacokinetic studies have demonstrated that extended infusions of MER over 3 hours (administered every 8 hours) are sufficient to achieve the targeted fT > MIC.17

**DATA IN PEDIATRICS**

Although several studies have been conducted to determine whether any clinical benefit exists for prolonged infusion β-lactams in adults, this issue has not yet been addressed in clinical trials in the pediatric population. Because children exhibit increased drug clearance, this is a population that may particularly benefit from prolonged β-lactam infusions. The potential pharmacodynamic benefit of prolonged infusions of β-lactams in children ages 2 and 12 years of age has been demonstrated in a Monte Carlo simulation.6 This simulated study demonstrated that extended or continuous infusion regimens improved the probability of attaining fT > MIC for the various β-lactams when compared with traditional dosing. The benefit was most noticeable at MICs that approached the susceptibility breakpoints. A well-designed, prospective study employing these administration strategies in pediatric patients is warranted. Currently, dosing recommendations for prolonged infusion β-lactams are not available for children. In our institution, prolonged infusion strategies for β-lactams are considered for children with serious Gram-negative infections as a result of pathogens with high MICs, in the setting of normal renal function. We have used similar infusion times as reported in adult studies using the maximum milligram per kilogram dose in combination with an aminoglycoside (eg, PIP-TAZ 100 mg/kg/dose every 6 hours infused over 4 hours; CFZ or CEF 50 mg/kg/dose every 8 hours infused over 8 hours; and MER 40 mg/kg/dose every 8 hours with each dose infused over 3 hours).

**CONCLUSION**

Optimizing the pharmacokinetics-pharmacodynamics of currently available antibiot- ics is necessary in the era of multidrug-resistant organism infections. Known β-lactam pharmaco- dynamics support the concept of prolonged infusion to maximize fT > MIC, but clinical data on the efficacy of prolonged β-lactam infusion are limited. To date, this topic has been mostly evaluated in small, unblinded, single-center studies, and no consistent benefit has been demonstrated. Therefore, indications for prolonged β-lactam infusion should be considered on a case by case basis.

Patients with susceptible pathogens can achieve an fT > MIC and clinical cure with traditional intermittent β-lactam administration, but prolonged infusion is a reasonable option for patients without renal impairment and severe infections secondary to pathogens with high MIC values. Patients with renal dys- function are likely to have higher serum drug concentrations due to decreased clearance regardless of the infusion strategy. It is important to note that in most published studies of pro- longed β-lactam infusion, the bacterial isolates had MICs in the susceptible range, and there is little difference between intermittent and pro- longed administration of β-lactams in achiev- ing fT > MIC with low MICs. However, when less susceptible organisms are present, the like- lihood for treatment failure increases with in- termittent dosing.

Although continuous infusion is a ra- tional method for optimizing fT > MIC, barriers that may preclude its use include limited intravenous access, potential incom- patibility with other coadministered drugs, stability of the drug over prolonged periods, and ambulatory patient status. Some of these issues may be circumvented with extended infusion protocols. A large, multicenter RCT is needed to further substantiate the benefits of prolonged infusion β-lactams.

**REFERENCES**


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FIGURE 1. Achievable serum concentrations with intermittent β-lactam infusion compared with extended infusion and continuous infusion.