Reply to Rhodes et al

To the Editor—We read with interest the letter from Rhodes et al [1] in response to the DALI study (Defining Antibiotic Levels in Intensive Care Unit Patients) published earlier this year in Clinical Infectious Diseases [2]. The authors provided their own loading dose pharmacokinetic/pharmacodynamic simulations before both extended and continuous infusions. In contrast to standard probability of target attainment figures that provide results over a dosing interval or 24-hour period, the authors provided data for the first 120 minutes of therapy. Unsurprisingly, the authors showed that a loading dose is associated with improved achievement of target antibiotic exposures over this time period. Although investigation of this issue was not an aim of the DALI study [3], we support the sentiments of Rhodes et al and agree that loading doses before extended or continuous infusions are essential.

However, we query whether the implications of not using loading doses may be worse than actually suggested. We note that the authors performed simulations using models that were not derived during first-dose pharmacokinetics, which may in fact result in even lower drug exposures in the first 120 minutes of therapy. Furthermore, the Lomaestro et al [4] model used by Rhodes et al [1] included data for volunteers who were mostly healthy (no critically ill patients), heightening the likelihood that the delay to therapeutic concentrations could be even greater for patients with altered beta-lactam pharmacokinetics [5]. As such, we warn that the delay to therapeutic exposure may be even more significant.

Loading doses have been widely used for continuous infusions of beta-lactam antibiotics [6, 7], although they were not always used in previous studies [8]. Data for use of loading doses in extended infusions are less common [9], but the rationale for their application should not be underestimated. First, the possible “dead space” in intravenous lines means that with slower infusions, the delay for the patient to receive any antibiotic increases. Second, given that most infections occur in the interstitial fluid of tissue, we would hypothesize that a higher initial plasma concentration would provide a concentration gradient that enables more rapid achievement of therapeutic concentrations at the site of infection [10]. Third, for patients with augmented renal clearance (ARC) [11], a lack of loading dose further delays achievement of therapeutic concentrations. This may indeed be a contributory reason for the failure in a recent phase 3 study of doripenem administered by extended infusion in ventilator-associated pneumonia where, in particular, ARC patients receiving doripenem with creatinine clearances >150 mL/min had a significantly greater risk of clinical failure [12].

We support the conclusions of Rhodes et al and suggest that a danger is posed to patients if loading doses are not used before continuous or extended infusions.

Notes

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