Appropriate Comparators for Alternate Dosing Strategies

To the Editor—Clinical studies remain the gold standard for validation of pharmacokinetic-pharmacodynamic models that attempt to define the complex interactions among antibiotics, infecting organisms, and the human host. Comparison with a currently accepted and proven therapy is an important consideration. Prospective, randomized, controlled trials of piperacillin-tazobactam for the treatment of nosocomial pneumonia have included dosing regimens of 4.5 g administered every 6 h and 3.375 g administered every 4 h with concomitant aminoglycoside therapy [1, 2]. We are unaware of any guidelines that recommend or prospective clinical trials that use 3.375 g of piperacillin-tazobactam administered every 6 h to treat the specific indication nosocomial pneumonia or infection due to the specific organism Pseudomonas aeruginosa.

In the study by Lodise et al. [3], the authors proposed an extended-infusion dosing method based on Monte Carlo simulation. It was expected that the extended dosing interval would provide greater time above MIC for P. aeruginosa. The results demonstrated a lower 14-day mortality rate in patients who received the extended infusion regimen. The authors recognize some limitations of their study, but other important limitations, including clinically unproven comparator dosing and inconsistent concomitant therapy, are not addressed.

In this study, there were 92 patients in the intermittent-infusion arm, with 88 patients receiving 3.375 g every 6 h. Approximately one-half of the patients in each arm had respiratory tract isolates, and although it is not clear how many of these isolates were from patients with ventilator-associated pneumonia, hospital-acquired pneumonia, or health care-associated pneumonia, the current recommended treatment of nosocomial pneumonia with piperacillin-tazobactam is 4.5 g administered every 6 h with concomitant aminoglycoside therapy [4]. Furthermore, the percentage of patients receiving an aminoglycoside or fluoroquinolone in each arm was similar; however, the inclusion criteria only required that an aminoglycoside or fluoroquinolone be given within 96 h after a positive culture result and continued for at least 24 h. In fact, the majority of patients received no concomitant therapy on the basis of these criteria.

Studies comparing extended and continuous infusion for time dependent antimicrobials are important, especially for those organisms associated with frequent lethal outcomes and variable or broad MIC distributions near breakpoint. We agree with the authors that dosing comparison through randomized clinical trials is optimal to prevent the introduction of bias into the conclusions. Future pharmacodynamic modeling should be validated with clinical outcomes using clinically proven dosing regimens. The results of this study should be interpreted cautiously in the face of these limitations.

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References


Reply to Tucker and Wu

To the Editor—The letter by Drs. Tucker and Wu [1] notes several issues regarding our recent study comparing extended and intermittent infusion of piperacillin-tazobactam [2]. When extraneous concerns are removed, there are 2 main issues that are raised: (1) the study was not a randomized, controlled trial, and (2) the dosages and schedules used for a number of patients in the study were not in concordance with the package insert [3].

The purpose of our study was to compare extended versus intermittent infusion piperacillin-tazobactam against Pseudomonas aeruginosa infection before and after implementation of a hospital-wide substitution program. Thus, our study was a deliberate departure from clinical trials and was not intended to mimic the designs of the nosocomial pneumonia study performed by Wyeth and reported in the piperacillin-tazobactam package insert [3–5]. Our intent was to quantify hard study data...