Brief Report

Influence of Culture Site–Specific MIC Distributions on the Pharmacokinetic and Pharmacodynamic Properties of Piperacillin/Tazobactam and Piperacillin: A Data Analysis

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ABSTRACT

Background: Investigators who perform pharmacokinetic/pharmacodynamic (PK-PD) modeling with Monte Carlo simulation have historically not stratified microbiological data by culture site. This lack of stratification might be problematic if susceptibility patterns differ among sites and might lead to differences in PK-PD.

Objective: This study compared the PK-PD of 2 antimicrobial regimens against 5 gram-negative bacterial species from 3 culture sites.

Methods: This data analysis was performed at the Department of Pharmacology, The University of Texas Health Science Center, San Antonio, Texas. Blood, pulmonary (ie, bronchial, endotracheal, lung, respiratory, sputum, and tracheal secretions), and wound distributions of MICs were extracted from the 2002 Intensive Care Unit Surveillance System database. Bacteria included *Acinetobacter baumannii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.* The PK properties of piperacillin/tazobactam (3.375 g every 4 hours) and piperacillin (3 g every 4 hours) were obtained from studies in healthy volunteers. Monte Carlo simulation was used in 10,000 patients for each antimicrobial-bacteria-culture site combination. The cumulative fraction of response (CFR) for a free percentage time above the MIC of ≥50% was determined for each combination, and a clinically significant difference was defined a priori as ≥10%.

Results: Data from 2408 pulmonary, 490 blood, and 242 wound isolates were included. For piperacillin/tazobactam, the CFR varied <10% by culture site in all 5 bacterial species. Site-specific differences were noted in MIC_{50} for piperacillin versus *E cloacae* and *E coli* and MIC_{90} for piperacillin/tazobactam versus *K pneumoniae* and *P aeruginosa.* Likewise, for piperacillin, the CFR was similar among the 3 culture sites for *P aeruginosa.* However, the CFR for piperacillin varied by ≥10% for *A baumannii* (blood > wound), *E cloacae* (pulmonary > blood), *E coli* (pulmonary and blood > wound), and *K pneumoniae* (wound > blood).

Conclusions: The PK-PD models based on PK properties found in healthy humans and site-specific MIC distributions in this study suggest that for piperacillin, culture-site differences subsequently resulted in CFR differences that exceeded a predetermined level of clinical significance. Furthermore, these data suggest that traditional reporting strategies for microbiological data (ie, MIC_{50} and MIC_{90}) might fail to adequately characterize the MIC population. (*Clin Ther.* 2006;28: 1035–1040)

Key words: pharmacokinetics-pharmacodynamics, β-lactams, culture site, Monte Carlo simulation.

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INTRODUCTION

Pharmacokinetic/pharmacodynamic (PK-PD) studies integrate in vivo PK and in vitro microbiological data (eg, MIC) to predict clinical success. Incorrect assumptions regarding either component might compromise the integrity of PK-PD analyses. Findings from a prior PK-PD modeling study[1] suggest that the microbiological data appear to have a greater impact on PK-PD analyses than do PK parameters, such as Vd, $t_{1/2}$, and protein binding; hence, the manner by which MIC data are integrated into PK-PD models is of the utmost importance. One advantage of contemporary PK-PD studies that use the Monte Carlo simulation is that they integrate the entire MIC distribution rather than using only a single value (eg, median MIC [MIC_{50}], minimum concentration needed to inhibit 90% of isolates [MIC_{90}], percentage of susceptible isolates). This approach enables more precise estimates and might expose nuances of the distribution that are not fully communicated when microbiological data are represented by single values.[2]

A MEDLINE search (key terms: *piperacillin, tazobactam, pharmacokinetics,* and *human*; years: 2000–2005), revealed several PK-PD studies[3–5] that derived MIC distributions from large antimicrobial surveillance programs and no studies that stratified isolates by culture site. These findings might reflect a desire to incorporate the greatest number of isolates available, an inability to stratify cultures by site due to a lack of clinical data, or an underappreciation of the impact of culture site–specific differences in MIC distributions. If isolates are not stratified by culture site, investigators make an underlying assumption that MICs are relatively consistent among culture sites or, alternatively, that small differences in culture site–specific MIC distributions will not result in notable differences in PK-PD. The present study determined whether MICs differ by culture site for gram-negative bacteria and used PK-PD modeling with Monte Carlo simulation to assess the impact of the entire culture site–specific MIC distribution on the PK-PD of piperacillin/tazobactam and piperacillin.

MATERIALS AND METHODS

This data analysis was performed at the Department of Pharmacology, The University of Texas Health Science Center, San Antonio, Texas. MIC distributions from blood, pulmonary (ie, bronchial, endotracheal, lung, respiratory, sputum, and tracheal secretions), and wound cultures were extracted from the 2002 Intensive Care Unit Surveillance System (ISS) database (Merck & Co., Inc., Rahway, New Jersey).[6,7] The ISS database is a multiyear, national survey of antimicrobial resistance rates among aerobic gram-negative bacteria recovered from patients in intensive care units (ICUs) in the United States.[6,7] Gram-negative bacteria were *Acinetobacter baumannii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.* Distributions with ≥20 clinical isolates per culture site were used. MIC_{50}, MIC_{90}, and percentages of susceptible isolates were calculated according to the standards of the Clinical and Laboratory Standards Institute (CLSI).[8] In accordance with these standards, a breakpoint of 16 μg/mL was used for all gram-negative bacteria, except for *P aeruginosa* (64 μg/mL).[8] Piperacillin/tazobactam and piperacillin were selected as the antimicrobial regimens because their broad spectrum of activity permitted a large number of comparisons for several bacterial species. Prior studies[9,10] have found that the PK-PD profile for piperacillin/tazobactam 3.375 g every 4 hours is better than 3.375 g every 6 hours, 4.5 g every 6 hours, and 4.5 g every 8 hours; therefore, the present study modeled piperacillin/tazobactam 3.375 g every 4 hours and piperacillin 3 g every 4 hours. Vd at steady state (Vd_{ss}) (mean [SD], 0.15 [0.02] L) and terminal $t_{1/2}$ ($t_{1/2\beta}$) (mean [SD], 0.76 [0.11] hour) were obtained from a study in healthy adult volunteers.[11] Protein binding was obtained from a piperacillin/tazobactam PK study[1] that stated that the protein binding for both piperacillin and tazobactam was 30% and that the protein binding of each was unaffected by the presence of the other. All PK parameters reflect values measured in serum. In the PK-PD models, Vd_{ss} and $t_{1/2\beta}$ varied based on a logarithm-normal distribution, whereas protein binding varied from 20% to 40% based on a uniform distribution. The entire site-specific MIC distributions were integrated using a custom distribution. Crystal Ball 2000.2 Professional software (Decisioneering, Inc., Denver, Colorado) was used to conduct Monte Carlo simulations with 10,000 patients for each antimicrobial-bacteria-culture site combination. The cumulative fraction of response (CFR) was calculated for a free percentage time above the MIC (f%T>MIC) based on a previously published 1-compartment PK-PD equation.[12] The chosen PK-PD target was a f%T>MIC≥50%,[13,14] and a clinically significant difference was defined a priori as ≥10%.