Use of Monte Carlo Simulation to Assess the Pharmacodynamics of β-Lactams Against *Pseudomonas aeruginosa* Infections in Children: A Report from the OPTAMA Program

Jennifer M. Ellis, PharmD[1]; Joseph L. Kuti, PharmD[2]; and David P. Nicolau, PharmD, FCCP[2]

[1]University of Connecticut, School of Pharmacy, Storrs, Connecticut; and [2]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut

ABSTRACT

Background: Assessing the likelihood of achieving bactericidal pharmacodynamic exposures against *Pseudomonas aeruginosa* with intravenous antimicrobial regimens would provide insights into the selection of empiric therapy in the pediatric population.

Objective: The objective of this study was to use pharmacodynamic modeling to determine the likelihood of various pediatric antibiotic regimens achieving bactericidal exposures against *P aeruginosa* in children.

Methods: Minimum inhibitory concentrations (MICs) were determined for meropenem (20 and 40 mg/kg q8h), imipenem (15 and 25 mg/kg q6h), ceftazidime (50 mg/kg q8h), cefepime (50 mg/kg q8h), and piperacillin/tazobactam (75 mg/kg q6h) against *P aeruginosa* isolates from 2 pediatric institutions. A 5000-patient Monte Carlo simulation was performed to predict attainment of pharmacodynamic targets against *P aeruginosa* for each of these regimens in a population of 10-year-olds. Optimal regimens were defined as those that had a ≥90% likelihood of attaining target exposures.

Results: At institution 1, high-dose imipenem, high-dose meropenem, and ceftazidime achieved bactericidal pharmacodynamic exposures (likelihood of target attainment: 94%, 92%, and 92%, respectively). No other regimen was associated with a high probability of attaining bactericidal exposure (low-dose imipenem, 87%; cefepime, 85%; low-dose meropenem, 84%; piperacillin/tazobactam, 60%). At institution 2, no regimen was associated with a high likelihood of attaining bactericidal exposure; the calculated probabilities were cefepime, 78%; ceftazidime, 65%; high-dose meropenem, 58%; high-dose imipenem, 57%; low-dose imipenem, 54%; low-dose meropenem, 47%; and piperacillin/tazobactam, 47%. A lack of agreement between attainment of bactericidal exposures and percent susceptibility was apparent for many of the regimens.

Conclusions: Few regimens demonstrated a high likelihood of achieving bactericidal exposures against *P aeruginosa* at these institutions. Importantly, percent susceptibility overestimated attainment of the bactericidal target for some regimens, suggesting that further study is necessary in pediatric patients. The findings of this study highlight differences in target attainment and MIC distributions between institutions, emphasizing the importance of using institution-specific data when selecting empiric antimicrobial therapy. (*Clin Ther.* 2005;27:1820–1830) Copyright © 2005 Excerpta Medica, Inc.

Key words: pharmacodynamic, antimicrobial, pediatric, *Pseudomonas aeruginosa.*

INTRODUCTION

Pseudomonas aeruginosa is a common bacterium associated with pneumonia and bloodstream and urinary tract infections in children.[1] Infections associated with *P aeruginosa* account for almost 25% of all infections in the pediatric intensive care unit.[2,3] Mortality rates associated with *P aeruginosa* infections in children are higher than for any other common bacteria.[2,3] Therefore, it is essential to select optimal empiric antibiotic therapy in the pediatric population.

Distinct differences in antimicrobial resistance have been described in the pediatric population compared

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with the adult population.[3,4] These differences have been attributed to differing medical conditions, antimicrobial utilization, and hospital exposures in these populations.[3] Data regarding patterns of resistance among *P aeruginosa* isolates from children have only recently been described[3,4]; however, trends in minimum inhibitory concentration (MIC) distribution and resistance over time are still not well defined. Furthermore, specific resistance rates may vary depending on geographic location, type of infection, age of the pediatric patient, and type of unit in which isolates were collected.[1,3–5]

Correlations between the microbiologic outcome, medication exposure, and MIC have been reported in several studies in both children and adults.[6–9] Such pharmacodynamic relationships provide insight into the killing characteristics of antimicrobial agents; however, the type of relationship varies among antimicrobial classes. Specifically, the β-lactams kill best when free drug concentrations are maintained above the MIC for a particular proportion of their dosing interval (%T>MIC).[6] The pharmacodynamic exposure necessary for bactericidal activity also varies within the β-lactam class. Carbapenems demonstrate bactericidal activity at ~40% T>MIC, whereas penicillins and cephalosporins require at least 50% T>MIC for bactericidal activity.[10] Choosing an antimicrobial regimen that provides the greatest likelihood of achieving the required pharmacodynamic exposure not only will lead to optimal clinical and microbiologic outcomes, but also may reduce the likelihood of selecting resistant pathogens and therefore help limit the emergence of further resistance.[10]

The objective of this study was to use pharmacodynamic modeling to determine the likelihood of various pediatric intravenous antibiotic regimens achieving bactericidal exposures against *P aeruginosa* in children. As in other OPTAMA (Optimizing Pharmacodynamic Target Attainment using the MYSTIC [Meropenem Yearly Surveillance Test Information Collection] Antibiogram) programs, this study used a Monte Carlo simulation to consider variability in both antimicrobial pharmacokinetic parameters in patients and the susceptibility of a pathogen or pathogens.[11–13] As the MYSTIC surveillance study included few pediatric isolates and full MIC distributions specific to the pediatric population were not available in the literature, the study used prospectively determined MICs for *P aeruginosa* isolates obtained from patients at 2 children's hospitals to determine the probability of achieving pharmacodynamic target exposures with currently used antimicrobial regimens.

MATERIALS AND METHODS

Microbiology

P aeruginosa isolates were obtained from the collections of 2 pediatric tertiary-care institutions in the United States. One institution has 129 beds and the other has 226 beds; both have a level III neonatal intensive care unit and a 16-bed medical/surgical pediatric intensive care unit. Institution 1 required infectious diseases approval for the use of cefepime and meropenem, whereas during the collection period, institution 2 had an open formulary (subsequently converted to a meropenem-preferred formulary). At institution 1, 43 clinical isolates of *P aeruginosa* were obtained from infants and children (age range, ≤1–17 years) hospitalized between October 2003 and November 2004; ~25% of isolates were from the pediatric intensive care unit. At institution 2, 44 isolates were obtained from patients hospitalized in the pediatric intensive care unit (age range, <1–33 years) from July 2002 to August 2004; 5 of the isolates were from patients aged >18 years, all with chronic conditions originating in childhood, such as cri du chat syndrome, cerebral palsy, and congenital cardiac conditions. Multiple *P aeruginosa* isolates obtained from the same patient within a 1-week period with MICs within 1 dilution of one another were considered duplicates and were excluded.

MICs were determined by Etest (AB Biodisk, Solna, Sweden) or via computer-aided disk diffusion (BIOMIC, Giles Scientific, Santa Barbara, California) for meropenem, imipenem, ceftazidime, cefepime, and piperacillin/tazobactam. When MICs were read at either extreme of the spectrum, the next-lowest or next-highest dilution was recorded. This was required only for the carbapenems for certain isolates read by computer-aided disk diffusion; specifically, at institution 2, MICs read as <1 μg/mL for imipenem were reported as 0.5 μg/mL, and MICs read as <0.5 μg/mL for meropenem were reported as 0.25 μg/mL. Percent susceptibilities were calculated according to Clinical and Laboratory Standards Institute (CLSI, formerly National Committee for Clinical Laboratory Standards) guidelines for each antimicrobial agent against *P aeruginosa*.[14] The MIC distribution for each of the antimicrobial agents at the 2 institutions is shown in **Table I.**