Pharmacodynamically Guided Levofloxacin Dosing for Pediatric Community-Acquired Pneumonia

Joshua D. Courter,1 Kristen R. Nichols,2,3 Christina Kazazian,4 Jennifer E. Girotto4

1Division of Pharmacy, Cincinnati Children’s Hospital Medical Center, Ohio, 2Butler University College of Pharmacy and Health Sciences, 3Riley Hospital for Children at Indiana University Health, Indianapolis, 4University of Connecticut School of Pharmacy, Storrs, and 5Connecticut Children’s Medical Center, Hartford

Background. Oral levofloxacin is recommended as a preferred treatment for infection with Streptococcus pneumoniae with a penicillin minimum inhibitory concentration (MIC) of ≥4 µg/mL and as an alternative for infection with S pneumoniae with a penicillin MIC of ≤2 µg/mL. To investigate the current dosing recommendations and create a pharmacodynamically guided regimen, a Monte Carlo simulation was performed.

Methods. The simulation included a previously published 1-compartment model, and incorporated a formula that takes into account age-appropriate weights for hospitalized patients. Three different dosing regimens, including community-acquired pneumonia guideline dosing, inhalational anthrax dosing, and a pharmacodynamically guided regimen, were assessed. The probability of target attainment was described as the proportion of patients who achieve an unbound-drug area under the concentration–time curve over 24 hours divided by the MIC above 33.7 µg/mL per hour. Microbiologic data from 2 stand-alone pediatric tertiary care centers were included.

Results. Guideline-recommended doses of levofloxacin seem to produce suboptimal exposure in patients aged 5–14 years for pneumococci with an MIC of 1 µg/mL. Anthrax dosing was suboptimal in patients aged <5 years and in those aged >15 years. The pharmacodynamically guided regimen maintained a probability of target attainment of >90% for all age groups without producing peak concentrations higher than those previously described. None of the regimens attained the pharmacodynamic targets for a levofloxacin MIC of 2 µg/mL.

Conclusions. Current dosing recommendations were found to be suboptimal for specific age groups. A pharmacodynamically guided levofloxacin dosing regimen was determined, but it will need to be studied clinically for safety and tolerability.

Keywords. levofloxacin; Monte Carlo method; pneumonia; Streptococcus pneumoniae.

INTRODUCTION

Pneumonia is the leading infectious cause of mortality globally; it killed an estimated 935 000 children younger than 5 years in 2013 [1]. Streptococcus pneumoniae is the leading bacterial cause of pneumonia and was responsible for an estimated 741 000 deaths in this population in a single year [2]. In 2011, the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America released evidence-based practice guidelines for the management of community-acquired pneumonia (CAP) in infants and children older than 3 months [3]. In these guidelines, oral levofloxacin is recommended as a preferred treatment for infection with S pneumoniae with a penicillin minimum inhibitory concentration (MIC) of ≥4 µg/mL and as an alternative for infection with S pneumoniae with a penicillin MIC of ≤2 µg/mL.

The pediatric CAP guideline-recommended dosing is based on pharmacokinetic and clinical studies [6, 7]. Although previously studied clinically in pediatric patients, these doses have been predicted to produce a suboptimal AUC of 38.4 µg-hour per mL in patients aged 5 to <10 years [7]. We hypothesized that levofloxacin dosing according to the current pediatric CAP guidelines would not achieve the minimum target fAUC0–t/MIC for S pneumoniae in patients aged 5–10 years. To investigate the current dosing recommendations and create a pharmacodynamically guided regimen, a Monte Carlo simulation was performed.

METHODS

Previously recommended dosing regimens, including the highest of those recommended by the CAP guideline (20 mg/kg per day in 2 doses for children aged 6 months to <5 years and 10 mg/kg per day once daily for children aged 5–16 years; maximum daily dose, 750 mg) [3, 7] and a regimen approved for the treatment of inhalational anthrax (16 mg/kg per day in 2 doses for children who weigh <50 kg and 500 mg once daily for children who weigh ≥50 kg) [5, 8] were analyzed. A pharmacodynamically guided regimen was derived by using current
dosing standards with which a ≥90% microbiologic response was predicted. The lowest dose resulting in a 90% microbiologic response was simulated for each age group that demonstrated suboptimal response. For simulation purposes, all doses were treated as an intravenous infusion administered at a continuous rate over 1 hour.

**Pharmacokinetic Model**

A 1-compartment pediatric levofloxacin pharmacokinetic model was selected from previously published models that were created from pharmacokinetic data collected from 3 clinical studies that included 90 pediatric patients aged 6 months to 16 years [7, 8]. Total body clearance rates, incorporating body size and maturation and a covariate matrix, were estimated [8] by using the following equation: clearance rate = α x weight/(age + A_0)^β. Steady-state volumes of distribution were estimated by using published weight-normalized values from the same population [7]. The unbound fraction (f_u) was based on data from the levofloxacin package insert [5].

**Monte Carlo Simulation**

The Monte Carlo simulation was performed by using Crystal Ball Fusion Edition release 11.1.2.0.00 (Oracle, Redwood Shores, California). A 1-compartment intravenous infusion model was constructed in Microsoft Excel as previously described [9]. The variables used were as follows (mean ± standard error): α = 1.5 ± 0.34 mL/min per kg; β = 0.43 ± 0.06; and A_0 = 0.32 ± 0.18 years. Steady-state volumes of distribution were generated with a log-normal distribution according to previously published pharmacokinetic parameters, which were stratified according to age (mean ± standard deviation): 0.5–2 years, 1.56 ± 0.3 L/kg; 2–5 years, 1.5 ± 0.21 L/kg; 5–10 years, 1.57 ± 0.44 L/kg; 10–12 years, 1.44 ± 0.35 L/kg; and 12–16 years, 1.56 ± 0.53 L/kg [7]. The unbound fraction was varied as evenly distributed random values to the 10^-15 decimal place between 0.62 and 0.76 [5]. Patient weights were generated by using a previously published model for age-appropriate weights for hospitalized children [10]. Steady-state serum concentration–time profiles were simulated for 10 000 hypothetical pediatric patients between the ages of 0.5 and <16 years receiving each levofloxacin dosing regimen.

The F_AUC_24/MIC was calculated for a range of MICs in doubling dilutions between 0.008 and 128 µg/mL. Bactericidal target attainment was defined as an F_AUC_24/MIC of ≥33.7 µg-hour per mL. The number of simulated patients within each 6-month age-increment group who met the bactericidal target was divided by the total number of patients in each age group, which resulted in the probability of target attainment (PTA) for each given MIC.

**Microbiology**

To characterize the potential impact of these dosing regimens for the treatment of *S pneumoniae* infection, the pharmacodynamic PTA was put into context relative to potential MIC distributions encountered at stand-alone pediatric hospitals. The investigators at each site gained approval from their respective institutional review board. The MIC values and corresponding patient ages were collected from 2 stand-alone pediatric tertiary care hospitals, Riley Hospital for Children at Indiana University Health and the Cincinnati Children’s Hospital Medical Center, which have 304 and 598 beds, respectively. Only the first isolate was included if multiple isolates from a single patient existed, and only respiratory (ie, bronchoalveolar lavage fluid, pleural fluid, endotracheal tube, sputum) or invasive culture (ie, blood, cerebrospinal fluid, abscess) sites were included. Pneumococcal levofloxacin MIC values were determined by microtiter plates at institution 1 and by E-tests at institution 2.

Each culture was matched to the calculated PTA according to patient age and MIC. The patients were then grouped according to age (0.5 to <2, 2 to <5, 5 to <10, or 10 to <16 years) and institution. The average PTA was then determined for each group, resulting in cumulative fractions of response (CFR) that represent the likelihood of a specific antimicrobial regimen attaining bactericidal activity against an *S pneumoniae* isolate of unknown resistance for the given age group at each institution. Although a biologic response near 100% is preferred for more virulent pathogens, a PTA or CFR value of ≥90% was considered desirable for lower respiratory tract infection and is aligned with criteria previously established by the OPTAMA (Optimizing Pharmacodynamic Target Attainment using the MYSTIC Antibiogram) program [11].

**RESULTS**

The simulation resulted in an average of 312 patients for each 6-month age-increment group between the ages of 6 months and 16 years. The resultant pharmacodynamic indices are presented according to regimen and age group in Table 1. The dosing recommended by the CAP guideline produced a PTA of ≥90% in children aged 1 to <5 and in those aged ≥14 years when treating isolates with a levofloxacin MIC of 1 µg/mL. The lowest PTA for this regimen was seen in children 5 years of age, in 84% of whom bactericidal concentrations were not achieved when treating isolates with a levofloxacin MIC of 1 µg/mL. The inhalational anthrax dosing achieved bactericidal concentrations in ≥90% of children aged 5 to <15.5 years when treating isolates with a levofloxacin MIC of 1 µg/mL. The regimen fails to achieve bactericidal concentrations in 40% of children aged 6 months when treating isolates with a levofloxacin MIC of 1 µg/mL.

A pharmacodynamically guided regimen was determined according to age group: 6 months to <5 years, 12 mg/kg per dose every 12 hours; 5–14 years, 8 mg/kg per dose every 12 hours (maximum, 375 mg/dose); and 14–16 years, 10 mg/kg
per dose, once daily (maximum, 750 mg/day). This guided dosing achieved a PTA of >90% for children at all ages (6 months to 16 years) in isolates with a levofloxacin MIC of 1. It is important to note that none of the modeled regimens attained pharmacodynamic targets for the treatment of isolates with a levofloxacin MIC of 2.

Maximal serum concentrations were similar among the 3 dosing schemes; the mean ± standard deviation values were 6.8 ± 0.9, 7.4 ± 1.0, and 8.6 ± 0.8 µg/mL for the anthrax, CAP, and pharmacodynamically guided regimens, respectively.

The distribution of pneumococcal levofloxacin MICs over time is shown in Figure 2. The numbers of isolates, MIC<sub>50</sub> values, MIC<sub>90</sub> values, and percent susceptible are listed according to institution for each age group in Table 1. In addition, the CFR for each age group according to institution is listed in Table 1.

**DISCUSSION**

In 2011, the American Academy of Pediatrics recommended that the use of fluoroquinolones be limited to clinical situations

<table>
<thead>
<tr>
<th>Dosing Strategy</th>
<th>Population</th>
<th>Regimen</th>
<th>Total Area Under the Curve (AUC&lt;sub&gt;24h&lt;/sub&gt;[mcg/mL/hr])</th>
<th>Peak Serum Concentration (C&lt;sub&gt;max&lt;/sub&gt; [mcg/mL])</th>
<th>Probability of Target Attainment (PTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAP Guideline</strong></td>
<td>6 mo–&lt;5 yr</td>
<td>10 mg/kg Q12H</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td></td>
<td>5–&lt;10 yr</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td></td>
<td>10–16 yr</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>750 mg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td><strong>Inhalational</strong></td>
<td>Weight &lt; 50 kg</td>
<td>8 mg/kg Q12H</td>
<td>8 mg/kg Q12H</td>
<td>8 mg/kg Q12H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td></td>
<td>Weight ≥50 kg</td>
<td>500 mg Q24H</td>
<td>500 mg Q24H</td>
<td>500 mg Q24H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td><strong>Pharmacodynamically</strong></td>
<td>6 mo–&lt;5 yr</td>
<td>12 mg/kg Q12H</td>
<td>12 mg/kg Q12H</td>
<td>12 mg/kg Q12H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td></td>
<td>5 yr–&lt;14 yr</td>
<td>8 mg/kg Q12H</td>
<td>8 mg/kg Q12H</td>
<td>8 mg/kg Q12H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td></td>
<td>14 yr–16 yr</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>750 mg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>10 mg/kg Q24H</td>
<td>Probability of Target Attainment (PTA)</td>
</tr>
</tbody>
</table>

Figure 1. Simulated regimen and resultant pharmacodynamic indices. Abbreviations: AUC<sub>24h</sub>, area under the concentration–time curve over 24 hours; CAP, community-acquired pneumonia; C<sub>max</sub>, maximum serum concentration; MIC, minimum inhibitory concentration; PTA, probability of target attainment; Q12H, every 12 hours; Q24H, every 24 hours; SD, standard deviation.
The American Academy of Pediatrics recommends that the use of fluoroquinolones be limited to patients for whom there are no safe and effective alternatives [12]. This guidance is based largely on the risk for adverse joint, tendon, and neurologic effects, in addition to concerns for resistance. Because joint and tendon toxicities are exposure related in animal models, it may be possible that increased doses result in increased toxicity. Further study of the pharmacodynamically guided dosing regimen is needed to clinically assess safety and tolerability. Clinicians will need to weigh the risks and benefits of using levofloxacin for patients with CAP.

In reviewing the simulation results, no regimen reliably produced an adequate PTA at any patient age for a pneumococcal isolate with a levofloxacin MIC of 2. Consideration should be given to reassessing the breakpoint for levofloxacin against S pneumoniae. This recommendation is supported by a report of treatment failures for a levofloxacin MIC of 1 µg/mL in an adult on a dose of 500 mg once daily (AUC, ~55)

**Figure 2.** Distribution of pneumococcal isolate minimum inhibitory concentrations (MICs) of levofloxacin according to year at institution 1 (A) and institution 2 (B).

in which there are no safe and effective alternatives or when intravenous treatment can be avoided through their use [12]. Although the need for levofloxacin in treating CAP should be limited, its dosing should be optimized when used. Although a relationship between clinical outcomes and fAUC24/MIC target achievement in children has not been examined, a relationship in adults has been found. In a study of 58 adult patients with community-acquired respiratory tract infection, the microbiologic response rate was 100% when an fAUC24/MIC of >33.7 was achieved, but it was only 64% at an fAUC24/MIC of <33.7 [4]. It is important to note that the authors of this study described a potential imprecision caused by a few treatment failures included in the data set. An additional factor for consideration is that suboptimal levofloxacin fAUC24/MICs are associated with the emergence of resistance [13].

The chosen pharmacokinetic model was informed from 85 children with presumed or documented bacterial infection, 44 of whom were hospitalized [8]. Because the age–weight correlation model was also based on hospitalized children, both of the incorporated models should be representative of the population in which one might find the need to use levofloxacin for CAP [10]. The estimations of clearance and volume of distribution incorporated into the simulation were non-Bayesian estimations, and the simulation did not incorporate intrasubject or intersubject variability, which might have resulted in an underestimation of variability within a pediatric population. The model was validated by analyzing raw AUC values, which were similar to those reported from previous studies [7, 8]. Because the oral bioavailability of levofloxacin is approximately 99%, the findings of this analysis are likely applicable to oral regimens as well [5].

In previous studies of levofloxacin in children with pneumonia, only 14 of 405 patients who received levofloxacin had cultures that tested positive for S pneumoniae. This result, in combination with local data suggesting that the levofloxacin MICs of S pneumoniae isolates have been increasing in recent years, raises the question of what dosing would be adequate for current isolates (Figure 2). The pharmacodynamically guided dosing regimen evaluated in this study produced AUC values that should produce efficacy for patients from whom isolates with an MIC of 1 µg/mL are obtained. Safety of this regimen is anticipated, because peak concentrations were similar to those seen with once-daily 750-mg doses in adults (8.6 ± 1.86 µg/mL), but this assumption needs to be confirmed [5].

Because levofloxacin is excreted primarily unchanged in the urine, the glomerular filtration rate may better serve to predict its clearance in the presence of varying degrees of renal impairment [5]. Future pharmacokinetic studies should include a measure of renal function in models, because the results of this simulation cannot be extrapolated for use in patients with renal dysfunction. Because there were fewer isolates from patients aged ≥10 years included for CFR analysis, the true clinical impact of these different regimens may differ from those predicted in this population. Also, because the pneumococcal isolates were collected from the Midwest of the United States, there may be regional differences in CFR, which would not have been detected. In general, those who run future pediatric Monte Carlo simulations should consider responses across age groups as a continuum to identify suboptimal exposures within subsets of the population.

Because there were fewer isolates from patients aged ≥10 years included for CFR analysis, the true clinical impact of these different regimens may differ from those predicted in this population. Also, because the pneumococcal isolates were collected from the Midwest of the United States, there may be regional differences in CFR, which would not have been detected. In general, those who run future pediatric Monte Carlo simulations should consider responses across age groups as a continuum to identify suboptimal exposures within subsets of the population.

Because levofloxacin is excreted primarily unchanged in the urine, the glomerular filtration rate may better serve to predict its clearance in the presence of varying degrees of renal impairment [5]. Future pharmacokinetic studies should include a measure of renal function in models, because the results of this simulation cannot be extrapolated for use in patients with renal dysfunction. Because there were fewer isolates from patients aged ≥10 years included for CFR analysis, the true clinical impact of these different regimens may differ from those predicted in this population. Also, because the pneumococcal isolates were collected from the Midwest of the United States, there may be regional differences in CFR, which would not have been detected. In general, those who run future pediatric Monte Carlo simulations should consider responses across age groups as a continuum to identify suboptimal exposures within subsets of the population.
Current CAP guideline–recommended doses of levofloxacin seem to produce suboptimal exposures for pneumococci with a levofloxacin MIC of 1 µg/mL in patients aged 5–14 years. A pharmacodynamically guided levofloxacin dosing regimen could overcome this, although further studies of its safety and tolerability are needed. No studied regimens resulted in pharmacodynamic targets for a levofloxacin MIC of 2 µg/mL being attained, which suggests the need for caution when treating S pneumoniae infection with a levofloxacin MIC of >1 µg/mL.

Notes
Acknowledgments. We thank Dr. Catherine M. T. Sherwin and Dr. Samir S. Shah for their critical review of the manuscript.
Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References