Pharmacokinetics of Multiple-Dose Intravenous Clindamycin in Obese Children

MJ Smith, MD, MSCE; D Gonzalez, PharmD, PhD; AL Goldman, MD; R Vogel, MD; JE Sullivan, MD; MD Reed, PharmD; R Anand, PhD; K Martza, MS; K Bereznya, MPhD; PB Smith, MD, MHS; M Cohen-Wolkowicz, MD, PhD; K Watt, MD; on behalf of the Best Pharmacometrica for Children Act – Pediatric Trials Network

University of Louisville, Louisville, KY; University of North Carolina, Chapel Hill, NC; Children’s Mercy Hospital, Kansas City, MO; Northwestern University, Chicago, IL; Akron Children’s Hospital, Akron, OH; EMNES Corp, Rockville, MD; Duke University, Durham, NC.

Background
• The emergence of community-acquired meticillin-resistant Staphylococcus aureus (MRSA) has led to increased clindamycin use in the pediatric population
• Obesity increases the risk of recurrent and severe MRSA infections, and is also prevalent among children
• Clindamycin is a bephaphic drug that may distribute differently in obese vs. non-obese patients
• Pharmacokinetic (PK) data to guide clindamycin dosing in obese children are unknown

Methods
• PK samples were collected from three separate trials:
  – Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥25th Percentile (CLN01)
  – Pharmacokinetics of Antibiotics in Infants (STAP01)
  – PK samples from obese children in CLN01 and POP01 were analyzed using a previously developed clindamycin population PK model that included data from all 3 trials
• This structural one compartment PK model included an effect of total body weight (TBW) and age on clindamycin clearance (CL), and TBW on volume of distribution (V)
• Normal fat mass (FMF), free mass fat (FMF) and lean body weight (LBM) were explored as alternative measures of body size
• Obesity was defined as body mass index (BMI) ≥ 95th percentile for age and included as a dichotomous variable
• Empirical Bayesian estimates of parameters of obesity and non-obese patients were compared using the Wilcoxon rank-sum test
• The final PK model was used to predict the clindamycin dose in children that matched the exposure achieved with standard adult dosing (300 mg p/day every 8 hours)
• Clindamycin safety was assessed in CLN01

Results
• 419 PK samples from 220 children were included in the population PK model:
  – 208 samples from 128 children from CLN01
  – 265 samples from 178 children from POP01
  – 65 samples from 25 children from CLN01
• 76 children met the study definition of obesity, 13 from CLN01 and 63 from POP01
• Pharmacokinetic and clinical characteristics of these children are summarized in Table 1
• As compared to NFM, FMF and LBM, the use of TBW resulted in lower objective function value and was used as the measurement of body size in the final model
• 2/21 children in CLNS trial experienced 3 adverse events, none of which were attributed to clindamycin

Table 1: Characteristics of Obese Children

<table>
<thead>
<tr>
<th>Covariate</th>
<th>POP01* (N=53)</th>
<th>CLN01 (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.3 (2.2, 20.1)</td>
<td>13.5 (9.1-17.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.2 (12.8, 193.8)</td>
<td>76.4 (40.5, 224)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>147 (81-188)</td>
<td>155 (124-188)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.0 (18.9-46.7)</td>
<td>29.8 (23.7-34.3)</td>
</tr>
<tr>
<td>SCR (mg/dL)</td>
<td>0.6 (0.2-1.6)</td>
<td>0.6 (0.3-1.5)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>36 (15-165)</td>
<td>23 (16.5)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>33.5 (9.1-195)</td>
<td>26 (10.3-31.5)</td>
</tr>
<tr>
<td>TBL (mg/dL)</td>
<td>0.0 (0.1-0.1)</td>
<td>0.4 (0.2-3.8)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>2.9 (1.9-4.2)</td>
<td>3.4 (2.3-4.6)</td>
</tr>
</tbody>
</table>

Data presented as median (range)

Conclusions
• Clindamycin may be dosed based on total body weight (max dose 2.7 g/day) without dose adjustment based solely on obesity
• Clindamycin exposures using total body weight matched standard adult dosing
• Clindamycin was well tolerated in this population

Reference