Pharmacokinetics of Multiple-Dose Intravenous Clindamycin in Obese Children

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Background

- The emergence of community-acquired methicillin-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 lipophilic 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 ≥85th Percentile (CLN01)[1]
  - Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POP01)[2]
  - Pharmacokinetics of Antistaphylococcal Antibiotics in Infants (STA01)[3]
- 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 (NFM), free fat mass (FFM) and lean body weight (LBW) 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 for obese 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 (600 mg IV every 8 hours)
- Clindamycin safety was assessed in CLN01

[1] NICHD-2012-CLN01; clinicaltrials.gov #NCT01744730; IND# 115,396
[2] NICHD-2011-POP01; clinicaltrials.gov #NCT01431326; IND# 113,645
[3] NICHD-2012-STA01; clinicaltrials.gov #NCT01728363; IND# 115,396

Results

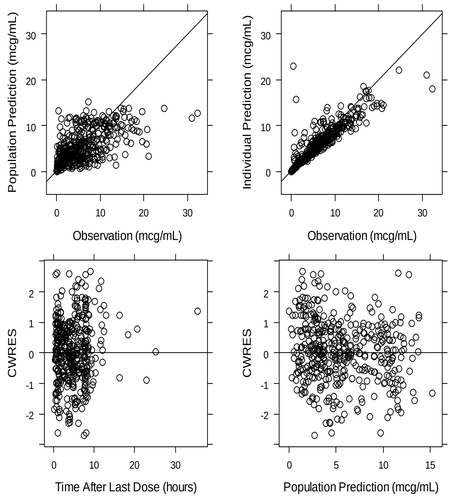
- 419 PK samples from 220 children were included in the population PK model:
  - 89 samples from 21 children from CLN01
  - 265 samples from 178 children from POP01
  - 65 samples from 21 children from STA01
- 76 children met the study definition of obesity; 13 from CLN01 and 63 from POP01. Demographic and clinical characteristics of these children are summarized in Table 1.
- As compared to NFM, FFM and LBW, 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 CLN01 trial experienced 3 adverse events, none of which were attributed to clindamycin

Table 1: Characteristics of Obese Children

Covariate	POP01* (N=63)	CLN01 (N=13)
Age (years)	12.4 (2.2-20.1)	13.5 (9.1-17.4)
Weight (kg)	61.2 (12.8-139.8)	76.4 (49.5-224)
Height (cm)	147 (81-188)	155 (134.4-188)
BMI (kg/m2)	29.0 (18.9-46.7)	28.9 (23.3-74)
SCR (mg/dL)	0.6 (0.2-1.6)	0.6 (0.3-1.5)
AST (U/L)	36 (15-165)	23 (8-151)
ALT (U/L)	33.5 (9-165)	28 (10-114)
TBIL (mg/dL)	0.6 (0.1-11)	0.4 (0.2-3.8)
Albumin (g/dL)	2.9 (1.9-4.2)	3.4 (2.3-4.6)

*Data presented as median (range)

Figure 1: Goodness-of-fit Plots, Final Model



$$CL\ (L/h) = 14.4*(WT/70)^{0.75}*(PMA^{3.32}/(39.8^{3.32}+PMA^{3.32}))$$
$$V\ (L) = 69.3*(WT/70)*(ALB/3.1)^{-0.78}$$

Figure 2: Box Plot of $AUC_{0\text{-}8,SS}$ Following Aged-based Clindamycin Dosing, Stratified by Obesity Status

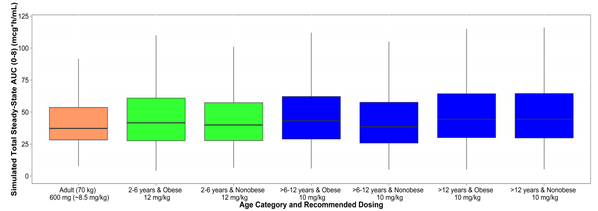


Figure 3: Box Plot of $C_{MAX,SS}$ Following Aged-based Clindamycin Dosing, Stratified by Obesity Status

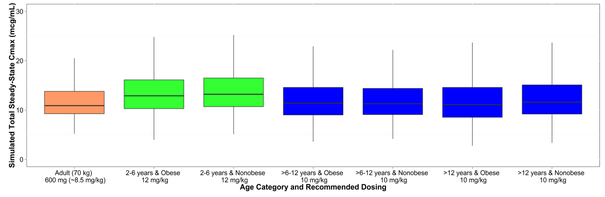


Table 2: Comparison of Empirical Bayesian Estimates for the Final Model Using TBW to Correct for Body Size

Age Categories	>2–6 Years*		>6–12 Years		>12 Years	
Parameters	Non-Obese (N=8)	Obese (N=12)	Non-Obese (N=15)	Obese (N=20)	Non-Obese (N=26)	Obese (N=44)
CL (L/h/kg)	0.24 (0.08-0.81)	0.27 (0.11-0.41)	0.34 (0.13-0.87)	0.21 (0.10-0.71)	0.23 (0.07-0.69)	0.19 (0.04-0.75)
CL (L/h/70 kg)	10.8 (3.7-36.1)	14.5 (5.6-21.5)	21.5 (7.2-54.3)	13.9 (6.3-43.7)	15.6 (5.1-43.2)	13.9 (3.2-43.9)
V (L)	16.0 (7.1-20.2)	19.0 (10.3-28.5)	32 (20.8-67.2)**	51.8 (32-68.9)	62.7 (25.7-102)**	92.7 (31.7-160)
V (L/kg)	0.82 (0.65-1.33)	0.94 (0.74-1.13)	1.01 (0.80-1.52)	1.0 (0.69-1.28)	0.96 (0.70-1.53)	0.95 (0.52-1.58)
Half-life (h)	2.4 (1.1-5.4)	2.6 (1.5-4.4)	2.2 (1.1-5.8)**	2.9 (1.3-5.5)	3.2 (1.4-7.1)	3.7 (1.2-9.8)

* Data presented as median (range)
** Significantly different using Wilcoxon rank-sum test

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

- Gonzalez D, et al. 2014. Use of Opportunistic Clinical Data and a Population Pharmacokinetic Model to Support Dosing of Clindamycin for Premature Infants to Adolescents. Clin. Pharmacol. Ther. 96: 429-37.

Acknowledgments

This work was funded under NICHD contract HHSN275201000003I for the Pediatric Trials Network.

D.G. receives research support through K23HD083465 from NICHD, and from the nonprofit organization Thrasher Research Fund (www.thrasherresearch.org).

P.B.S. receives salary support for research from the National Institutes of Health (NIH) and the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), NICHD (HHSN275201000003I and 1R01-HD081044-01) and the Food and Drug Administration (1R18-FD005292-01); he also receives research support from Cempra Pharmaceuticals (subaward to HHS0100201300009C) and industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp).

M.C-W. receives support for research from the NIH (1R01-HD076676-01A1), the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), the National Institute of Allergy and Infectious Disease (NIAID) (HHSN272201500006I and HHSN272201300017I), NICHD (HHSN275201000003I), the Food and Drug Administration (1U01FD004858-01), the Biomedical Advanced Research and Development Authority (BARDA) (HHSO100201300009C), the nonprofit organization Thrasher Research Fund, and from industry (CardioDx and Durata Therapeutics) for drug development in adults and children (www.dcri.duke.edu/research/coi.jsp).

K.W. receives support from NICHD (1K23HD075891) and the Pediatric Critical Care and Trauma Scientist Development Program (5K12HD047349) for his work in pediatric clinical pharmacology.

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