Obese Children Require Lower Doses of Pantoprazole Than Nonobese Peers to Achieve Equal Systemic Drug Exposures

Valentina Shakhnovich, MD[1], P. Brian Smith, MD, MHS, MPH[2], Jeffrey T. Guptill, MD, MA, MHS[3], Laura P. James, MD[4], David N. Collier, MD, PhD, FAAP[5], Huali Wu, PhD[2], Chad E. Livingston, MBA[6], Jian Zhao, PhD[7], and Gregory L. Kearns, PharmD, PhD[4], on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network*

Objective To assess appropriate pantoprazole dosing for obese children, we conducted a prospective pharmacokinetics (PK) investigation of pantoprazole in obese children, a patient population that is traditionally excluded from clinical trials.

Study design A total of 41 obese children (6-17 years of age), genotyped for *CYP2C19* variants *2, *3, *4, and *17, received a single oral dose of pantoprazole, ~1.2 mg/kg lean body weight (LBW), with LBW calculated via a validated formula. Ten post-dose pantoprazole plasma concentrations were measured, and PK variables generated via noncompartmental methods (WinNonlin). Linear and nonlinear regression analyses and analyses of variance were used to explore obesity, age, and *CYP2C19* genotype contribution to pantoprazole PK. PK variables of interest were compared with historic nonobese peers treated with pantoprazole.

Results Independent of genotype, when normalized to dose per kg total body weight, pantoprazole apparent clearance and apparent volume of distribution were significantly lower ($P < .05$) and systemic exposure significantly higher ($P < .01$) in obese vs nonobese children. When normalized per kg LBW, these differences were not evident in children ≥12 years of age and markedly reduced in children <12 years of age.

Conclusions LBW dosing of pantoprazole led to pantoprazole PK similar to nonobese peers. Additional factors, other than body size (eg, age-related changes in CYP2C19 activity), appear to affect pantoprazole PK in children <12 years of age. *(J Pediatr 2018;193:102-8).*

Trial registration ClinicalTrials.gov: NCT02186652

Childhood obesity has reached epidemic proportions.[1] Currently, 1 in 6 children in the US meets body mass index (BMI) criteria for obesity (BMI ≥95% for age).[1,2] The pediatric obesity epidemic brings a variety of comorbidities traditionally attributed to adult patients (eg, hypertension, type II diabetes mellitus).[3,4] Many of these obesity-related comorbidities represent life-long medical conditions that require pharmacotherapy; yet, limited guidelines exist for the appropriate dose-selection of medications in obese children.[5,6] An example of this challenge occurs with treatments for gastroesophageal reflux disease (GERD).

AE	Adverse event
AUC	Area under the concentration time curve
AUC_{inf}	AUC from time zero to infinity
AUC_{last}	AUC from time zero to the time of the last measurable concentration
BMI	Body mass index
CL/F	Apparent oral clearance
C_{max}	Peak plasma concentration
CYP	Cytochrome
CYP2C19	CYP P450 2C19 enzyme
CYP2C19	Gene that encodes the CYP P450 2C19 enzyme
EMs	Extensive metabolizers
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
IMs	Intermediate metabolizers
LBW	Lean body weight
PK	Pharmacokinetics
PM	Poor metabolizer
PPIs	Proton pump inhibitors
$t_{1/2}$	Half-life
TBW	Total body weight
T_{max}	Time to C_{max}
Vd/F	Apparent terminal-phase volume of distribution

From the [1]Divisions of Gastroenterology & Clinical Pharmacology, Toxicology and Therapeutic Innovation, The Children's Mercy Hospital, Kansas City, MO; [2]Department of Pediatrics, Division of Neonatal-Perinatal Medicine; [3]Department of Neurology, Division of Neuromuscular Medicine, Duke Clinical Research Institute, Durham, NC; [4]Department of Pediatrics, University of Arkansas for Medical Sciences Section of Clinical Pharmacology and Toxicology, Arkansas Children's Hospital, Little Rock, AR; [5]Department of Pediatrics and Center for Health Disparities, Division of General Pediatrics, East Carolina University, Greenville, NC; [6]Clinical Operations, Pediatric Trials Network; and [7]The Emmes Statistical Group, Rockville, MD

*List of additional members of the Best Pharmaceuticals for Children Act–Pediatric Trials Network is available at www.jpeds.com (**Appendix**).

Supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Pediatric Trials Network (NICHD-2012-PAN01). P.S. receives research support from the National Institutes of Health (NIH-1R21HD080606-01A1) and the National Institute of Child Health and Human Development (HHSN275201000003I). The other authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.10.011

Obese children are 6 times more likely than normal-weight peers to suffer from GERD,[7] a condition for which proton pump inhibitors (PPIs) have become the mainstay of therapy.[8] In 2010, over 500 000 pediatric prescriptions were filled for 1 PPI agent alone,[9] and PPIs remain in the top 12 drugs prescribed in the US.[10] Pantoprazole data published in adults suggest that dose escalation may be appropriate for obese patients receiving PPI therapy.[11] However, this strategy may be problematic and inappropriate in the pediatric obese population, where increasing the conventional weight-based dosing of PPIs (ie, mg/kg dosing based on total body weight, TBW) could lead to unnecessary systemic exposure that does not enhance efficacy, but rather predisposes patients to adverse events (AEs) associated with high-dose PPI therapy (eg, osteopenic fractures, gastrointestinal infections, pneumonia).[12-15] A better approach may be to first assess any pharmacokinetic differences between obese and nonobese peers, especially as the linearity of the relationship between PPI pharmacokinetics (eg, area under the concentration time curve, AUC) and pharmacodynamics (eg, intragastric pH) is less clear at higher PPI doses.[16] As substrates for the hepatic cytochrome (CYP) P450 2C19 (CYP2C19), the dose-exposure relationship for PPIs is markedly influenced by allelic variants in *CYP2C19*.[17-20] To further explore the association between obesity and *CYP2C19* genotype in pediatric patients, we conducted a controlled, open-label prospective trial in obese children with GERD, using pantoprazole as a model CYP2C19 substrate.[17] As 99% of metabolic processes in the human body, including drug clearance, take place in lean body tissues,[21] we hypothesized that pantoprazole dosing based on lean body weight (LBW) in obese children would lead to pantoprazole pharmacokinetics (PK) (eg, drug clearance and drug exposure) comparable to those previously reported in nonobese peers.[22]

Methods

This study was conducted in accordance with current US Food and Drug Administration (FDA) regulations and good clinical practice guidelines. It was approved by the Institutional Review Boards at The Children's Mercy Hospital, Duke University, Arkansas Children's Hospital, and East Carolina University (ClinicalTrials.gov: NCT02186652). Informed permission/assent and consent was obtained before the conduct of any study-related procedures.

This was a prospective, multicenter, open-label study of the PK and tolerability of pantoprazole in obese children (6-11 years of age) and adolescents (12-17 years of age) who, based on clinical criteria, required treatment with an acid-modifying agent for GERD. Obesity (BMI ≥95th percentile for age) and clinical diagnosis of GERD were confirmed at a screening visit, which included collection of blood for safety laboratory studies and DNA genotyping for CYP2C19 activity. All participants fasted at least 8 hours before study drug administration. On day 1 of the study, participants received a single oral dose of pantoprazole (commercially purchased, pantoprazole sodium, PROTONIX Delayed-Release Tablets, single-lot numbers: 228037AN for 20 mg tablets and 224201AN for the 40 mg tablets; Wyeth Pharmaceuticals, Inc, Philadelphia, Pennsylvania), according to a fixed-dose scheme based on LBW, so as not to exceed the maximum recommended pantoprazole dose. LBW was calculated using an established equation (Janmahasatian equation) for male and female children.[23] Children with LBW 20-25 kg received 20 mg pantoprazole, LBW 26-45 kg 40 mg, LBW 46-65 kg 60 mg, and LBW ≥66 kg 80 mg. Repeated blood samples, 1.0 mL each, were collected from participants via an indwelling intravenous catheter pre-dose (within 30 minutes of receiving pantoprazole) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours (±10 minutes) after pantoprazole dosing. For those participants with the poor metabolizer (PM) *CYP2C19* genotype and to better characterize the pantoprazole disposition profile in PM individuals, an additional PK sample was collected 12 hours after dosing. On day 10-13 of study, a follow-up phone call was conducted to assess the participant's general well-being and to collect any AEs.

All participants had a clinical diagnosis of GERD (ie, clinical symptoms consistent with GERD, evidence of erosive esophagitis on endoscopy, histopathology on esophageal biopsies consistent with reflux esophagitis, abnormal pH-metry consistent with acid reflux, or other tests and procedures consistent with GERD established at least 7 days before receipt of study drug), but were otherwise healthy. Specifically, those participants with diabetes mellitus, hepatic dysfunction (serum aspartate transaminase ≥150 IU/L, alanine transaminase ≥150 IU/L, total bilirubin ≥2.0 mg/dL, or alkaline phosphatase ≥600 IU/L), renal dysfunction (serum creatinine ≥2.0 mg/dL), infection with Hepatitis B or C, or pregnancy were excluded from the study. Those participants who received a dose of pantoprazole, lansoprazole, omeprazole, esomeprazole, or rabeprazole within 48 hours of receipt of study drug were excluded. Also excluded were participants who received the following concomitant medications (ie, known inhibitors or inducers of CYP2C19) within 7 days of study drug administration: fluoxetine, fluvoxamine, ketoconazole, ticlopidine, felbamate, topiramate, valproic acid, phenobarbital, carbamazepine, erythromycin, clarithromycin, grapefruit juice, verapamil, diltiazem, cimetidine, St. John's Wort, rifampin, or rifapentine.

PK variables relevant to drug disposition of pantoprazole were assessed as the study's primary endpoint (apparent peak plasma concentration [C_{max}], time of C_{max} [T_{max}], AUC, apparent terminal-phase volume of distribution [Vd/F], apparent total plasma clearance, and parent:metabolite ratios). Secondary endpoints included assessment of the relationship of nongenetic factors (eg, age, BMI) and genetic factors (eg, sex, *CYP2C19* genotype) to variability in drug disposition (ie, PK variables), as well as the safety of pantoprazole in obese children and adolescents.

To generate PK variables, all plasma samples were run in duplicate and the mean value used for analysis. Pantoprazole and pantoprazole-sulfone concentrations in plasma were quantified by the Pediatric Trials Network's central laboratory (OpAns, LLC, Durham, North Carolina) using a validated high-performance liquid chromatography tandem mass spectrometry assay. During method validation, accuracy and precision