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ARTICLE

Population Pharmacokinetics of Metoclopramide in Infants, Children, and Adolescents

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Metoclopramide is commonly used for gastroesophageal reflux. The aims of the present study were to develop a pediatric population pharmacokinetic (PopPK) model, which was applied to simulate the metoclopramide exposure following dosing used in clinical practice. Opportunistic pharmacokinetic data were collected from pediatric patients receiving enteral or parenteral metoclopramide per standard of care and these data were simultaneously fitted using NONMEM. Allometric scaling with body weight was included *a priori* in the model. Using the final model, the steady-state maximum concentrations ($C_{ss,max}$) and the area under the metoclopramide plasma concentration-time curve at steady state from 0 to 6 hours ($AUC_{ss,0–6h}$) were simulated following 0.1 or 0.15 mg/kg orally every 6 hours in virtual patients, and compared with previously reported ranges associated with toxicity or the efficacy for gastroesophageal reflux in infants. A two-compartment model with first-order absorption best characterized 87 concentration measurements from 50 patients (median [range] postnatal age of 8.89 years [0.01–19.13]). There were 20 infants (≤ 2 years), 9 children (2 years to age ≤ 12 years), and 21 adolescents (> 12 years). Body weight was the only covariate included in the final model. For > 75% of virtual patients, simulated $C_{ss,max}$ and $AUC_{ss,0–6h}$ estimates were within the range associated with efficacy for gastroesophageal reflux in infants; however, slightly lower exposures were predicted in virtual patients < 2 years. Our study suggests that a metoclopramide enteral dose of 0.1 mg/kg every 6 hours, which was previously recommended for pediatric patients, results in simulated exposure generally within suggested ranges for the treatment of gastroesophageal reflux.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Metoclopramide is a dopamine receptor antagonist used off-label in children for gastroesophageal reflux (GER), gastroparesis, nausea, and vomiting. Only one population pharmacokinetic (PopPK) study of metoclopramide has been performed, which included data from 47 patients with cancer 10–80 years of age.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study sought to characterize the PopPK of metoclopramide in pediatric patients, and to apply the model to evaluate simulated exposure following dosing used in clinical practice.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Our study suggests that a metoclopramide oral dose of 0.1 mg/kg every 6 hours, which was previously recommended for children, results in simulated exposure generally within suggested ranges for the treatment of GER.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This study contributes to our understanding of metoclopramide pharmacokinetics and dosing in the pediatric population. When the dose-response relationship of metoclopramide is further elucidated in future studies, our model could be used to further evaluate metoclopramide pediatric dosing.

Metoclopramide is a drug with prokinetic and anti-emetic properties that is prescribed for the treatment of gastrointestinal motility disorders, gastroesophageal reflux (GER), diabetic gastroparesis, nausea, and vomiting.[1,2] Metoclopramide injection is also used to facilitate small bowel intubation and radiological examination.[3,4]

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Metoclopramide's peripheral gastrointestinal prokinetic effects and central anti-emetic effects are mediated through antagonism of the dopamine 2 and 5-hydroxytryptamine type 3 receptors, as well as through 5-hydroxytryptamine type 4 receptor agonism.[5,6] In the United States, metoclopramide is not recommended by the US Food and Drug Administration (FDA) for use in children because its safety and effectiveness in this population have not been established except to facilitate small bowel intubation.[3] The FDA added a black box warning in metoclopramide's product label related to tardive dyskinesia, a serious adverse event involving involuntary and repetitive body movement. Extrapyramidal side effects (e.g., dystonic reactions, tardive dyskinesia, and parkinsonian-like symptoms) have also been reported with greater frequency in children compared with adults.[3] The European Medicines Agency recommends that metoclopramide not be used in children younger than 1 year of age, and as second-choice treatment in children older than 1 year for short-term use (up to 5 days) for the prevention of delayed nausea and vomiting after chemotherapy, as well as for the treatment of postoperative nausea and vomiting.[7] Although limited data are available to inform dosing in the pediatric population, metoclopramide is generally administered enterally or intravenously at a dosage of 0.1–0.2 mg/kg every 6–8 hours.[2,8–10]

The pharmacokinetics (PKs) of metoclopramide have been previously characterized in adults.[11–14] Metoclopramide undergoes metabolism via oxidation (primarily via cytochrome P450 2D6 (CYP2D6)) as well as glucuronide and sulfate conjugation.[15,16] Approximately 85% of the radioactivity of an orally administered dose is recovered in the urine, and half of it is present as parent or conjugated metoclopramide. Around 18–22% of the dose was recovered as free metoclopramide in urine.[4] Metoclopramide's elimination half-life in adults with normal renal function has been reported to be ~ 6 hours.[3,4] In adults with severe renal impairment, there is a reduction in metoclopramide clearance (CL), resulting in a prolongation in the terminal elimination half-life (7.7–17.8 hours), and a dose adjustment is recommended.[14] Only one population pharmacokinetic (PopPK) study of metoclopramide has been performed, which included data from patients 10–80 years old.[17] In this single PopPK analysis, a two-compartment model with linear elimination was used, and it was reported that body weight and serum alkaline phosphatase activity were significant covariates that explained interindividual variability (IIV) in the CL of metoclopramide. Given that metoclopramide is extensively metabolized in the liver, this suggests that metoclopramide's PKs may be impacted by liver function, which has been confirmed in studies of adults with liver cirrhosis.[18,19] Additional studies focused on characterizing the PKs of metoclopramide in adults have also been published.[11–13,18]

In the pediatric population, few studies have evaluated metoclopramide's PKs in neonates,[8] infants,[20] and children.[21] Whether the PKs of metoclopramide in adults and the pediatric population are similar remains unclear.[3] One study in preterm infants reported a greater metoclopramide weight-normalized CL (mean CL of 0.80 L/hour/kg) compared with adults (mean CL of 0.29–0.53 L/hour/kg).[8,11,17] Nevertheless, in two other studies performed in infants and children, the weight-normalized PK parameters were comparable to those in adults.[20,21]

Metoclopramide exposure targets for efficacy and toxicity have not been well established in adult or pediatric populations. Conflicting study results have been reported regarding the efficacy of metoclopramide as a prokinetic drug in children. In some studies, metoclopramide's favorable efficacy for the treatment of GER or vomiting was demonstrated in a pediatric population,[20,22–25] whereas in other studies it was shown that the metoclopramide treatment was ineffective in children.[9,26,27] One study in infants treated for GER suggested that the beneficial effects were associated with steady-state maximum concentrations ($C_{ss,max}$). In 6 infants with $C_{ss,max}$ ranging from 26 to 94 ng/mL, 4 of them had a 75% reduction in reflux time[20]; however, significant correlations were not found between metoclopramide exposures and pharmacodynamic parameters. Data evaluating the relationship between exposure and safety are also limited. One study reported that the metoclopramide plasma concentration measured in a child who developed dystonia after i.v. injection was 143 ng/mL.[21] The objectives of this study were to develop a PopPK model using opportunistic PK data collected from infants, children, and adolescents receiving metoclopramide and to apply the model to evaluate simulated exposure following dosing used in clinical practice.

METHODS

Data source

PK data used to develop the PopPK model were collected through the Pediatric Trials Network (PTN) Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care trial (POPS; ClinicalTrials.gov #NCT01431326; protocol: NICHD-2011-POP01), a multicenter, prospective study of the PKs of understudied drugs (including metoclopramide) administered to children (< 21 years of age) per standard of care. Patients receiving metoclopramide per standard of care as administered by their treating caregiver were enrolled across 12 sites. The study protocol was reviewed and approved by the institutional review boards of Duke University (coordinating center) and all participating sites, and all participants and participant parents/legal guardians provided written informed consent or assent as applicable. Subjects were enrolled in the study for up to 90 days, although subjects may be re-consented for enrollment into additional periods of up to 90 days. Exclusion criteria included failure to obtain consent or assent, or a known pregnancy, as determined by interview or testing, if available. Gestational age (GA) was collected for infants < 120 days postnatal age (PNA). Demographic and clinical variables were summarized based on the values at the time of first recorded dose (**Table 1** and **Table S1**).

Dosing and sample collection

For the PTN POPS study, dosing and PK sample collection times varied between patients. Dosing information was collected for up to eight doses prior to the sampling dose (last dose before first biological sample collection). Metoclopramide was given to patients orally or intravenously (bolus/infusion) or by other enteral routes of administration (nasogastric/nasojejunal/gastrostomy). At least 500 μL and

Table 1 Clinical and demographic data for 50 subjects

Characteristic[a]	Values[e]	No. subjects with data available (%)
GA (weeks)[b]	37.9 (29.5–40.5)	17 (34)
PNA (years)	8.9 (0.02–18.5)	50 (100)
Total body weight (kg)	23.5 (2.6–98.1)	50 (100)
Serum creatinine (mg/mL)	0.5 (0.2–1.1)	31 (62)
Creatinine clearance (mL/min/1.73 m^2)[c]	109.7 (5.0–225.1)	31 (62)
AST (U/L)	39.5 (17.6–116.0)	14 (28)
ALT (U/L)	39.5 (17.1–154.1)	12 (24)
Total bilirubin (mg/dL)	0.7 (0.2–15.2)	15 (30)
Albumin (g/dL)	3.5 (2.4–4.4)	17 (34)
BMI	19.0 (9.7–35.8)	50 (100)
Race		
White		35 (70)
African American		14 (28)
Unknown		1 (2)
Sex		
Male		26 (52)
Surgery[d]		3 (6)

ALT, alanine aminotransferase concentration; AST, aspartate aminotransferase concentration; BMI, body mass index; GA, gestational age; PNA, postnatal age; U/L, units per L.
[a]Descriptive statistics are calculated based on the values at the time of first recorded dose.
[b]For infants of < 120 days postnatal age (n = 17).
[c]Calculated by the Schwartz equation.
[d]The number of patients that had surgery within 24 hours prior to any sampling dose.
[e]Presented as median (5th–95th percentile).

up to ~ 3,000 µL of whole blood was collected per sample based on the patient's age. Because PTN POPS used an opportunistic study design, PK samples were collected optimally with standard of care laboratory collections, unless a parent/guardian provided consent to obtain PK samples for research purposes only. Standard of care laboratory assessments were recorded if samples were collected within 72 hours of a sampling dose of the drug. Blood samples were collected in EDTA-containing tubes. Plasma was separated by centrifugation (2,000 *g*) for 10 minutes at 4°C. Plasma samples were stored at –70°C or colder within 8 hours of collection.

Analytical methods

Plasma samples were sent to the PTN central laboratory (OpAns, LLC, Durham, NC) for storage and analysis. Sample preparation included an extraction procedure using methanol containing metoclopramide-d3 as internal standard. Extracts were analyzed by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) using positive ion multiple reaction monitoring. The HPLC-MS/MS conditions for analyzing metoclopramide were the following: column, Poroshell 120 EC-C18 column (3 × 50 mm i.d., 2.7 µm; Agilent, Santa Clara, CA); mobile phase A, 10 mM ammonium formate in deionized water containing 0.1% formic acid; and mobile phase B, methanol containing 0.1% formic acid; column temperature, 30°C. Linear gradient elution (**Table S2**) with a flow rate of 0.6 mL/min was used. The HPLC-MS/MS method was validated over the range 1–1,000 ng/mL and the lower limit of quantification was 1 ng/mL using a 10 µL aliquot of plasma. Accuracy and precision were within the FDA bioanalytical assay validation criteria.[28]

PopPK analysis

Metoclopramide plasma PK data were analyzed with a nonlinear mixed effects modeling approach using the software NONMEM (version 7.4.1; Icon Development Solutions, Ellicott City, MD). All data manipulation and visualization of diagnostic plots were executed using R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and RStudio version 0.99 (RSstudio, Boston, MA). Plasma concentration data collected following different routes of administration were simultaneously fitted. The first-order conditional estimation method with interaction was used for all model runs. One-compartment and two-compartment PK models with linear PKs were explored. First-order absorption with or without a lag time was evaluated. The impact of the route of administration (oral vs. other enteral routes) on the first-order absorption rate constant (K_a) and bioavailability (F) were also explored. For a two-compartment model with linear absorption and elimination, the estimated parameters were K_a, F, central compartment CL, central volume of distribution (V_c), peripheral volume of distribution (V_p), and intercompartmental clearance (Q).

Proportional, additive, and combined residual error models were explored. IIV in the PK parameters was assessed using an exponential relationship for all PK parameters (Eq. 1):

$$\mathrm{PAR}_{ij} = \theta_{\mathrm{Pop},j} \times \exp(\eta_{ij}) \quad (1)$$

where PAR_{ij} denotes the estimate of parameter j in the ith individual, $\theta_{\mathrm{Pop},j}$ is the population value for parameter j, and η_{ij} denotes the deviation from the average population value for parameter j in the ith individual with a mean of zero and a variance of ω^2.

Covariate selection

Actual body weight (WT) was assumed to be a significant covariate for CL, V_c, V_p, and Q, and was included in the base model. The parameter values were standardized to a 70 kg WT. The allometric relationship between WT and clearance parameters (CL and Q) was explored using a fixed exponent of 0.75. The relationship between WT and volume of distribution parameters (V_c and V_p) was characterized using a linear relationship (i.e., exponent fixed to 1).

Other relevant covariates investigated were continuous PNA, PNA groups A (group 1, < 1 month; group 2, 1 month to < 2 years; group 3, 2 to < 12 years; group 4, 12 to < 17 years; and group 5, 17 to < 21 years), PNA groups B (group 1, < 1 month; group 2, ≥ 1 month), GA, postmenstrual age (PMA), surgery (within 24 hours prior to the dose), obese status, body mass index, serum albumin, serum creatinine (SCr), creatinine clearance (estimated by the Schwartz equation[29,30]), aspartate aminotransferase, alanine aminotransferase, and bilirubin. Relevant

covariates were selected on the basis of physiological relevance and visual inspection of the individual deviations from the typical parameter values (ETA) vs. covariates. Missing covariate values were replaced by the population median values, whereas missing SCr levels were imputed as the median values for each PNA group. For participants with nonmissing laboratory records, including for SCr, values were imputed using the closest valid laboratory record. Laboratory records were considered valid if collected within 72 hours of a sampling dose. For participants with no valid laboratory records available, values were imputed using the median of the first valid value for each participant. The WT value used was the most recent measured weight for each record.

Linear, power, and sigmoidal maximum effect (E_{max}) maturation functions were tested to characterize the relationship between age (PNA, PMA, and GA) and CL. With the exception of WT and age, all other continuous covariates were tested using Eq. 2, whereas for categorical covariates, the relationship shown in Eq. 3 was used.

$$\mathrm{PAR}_{ij} = \theta_{\mathrm{Pop},j} * \left(\frac{\mathrm{cov}_i}{\mathrm{cov}_m}\right)^{\theta_{\mathrm{cov}}} \quad (2)$$

$$\mathrm{PAR}_{ij} = \theta_{\mathrm{Pop},j} * \theta_{\mathrm{cov},n} \quad (3)$$

where PAR_{ij} denotes the estimate of parameter j in the ith individual; $\theta_{\mathrm{Pop},j}$ is the population value for parameter j; cov_i denotes the individual covariate value; cov_m is the population median covariate value; θ_{cov} represents the covariate effect; and $\theta_{\mathrm{cov},n}$ represents covariate effect of the n^{th} category.

A forward inclusion ($P < 0.05$ and change in objective function value (OFV) > 3.84) and backward elimination ($P < 0.01$ and change in OFV > 6.64) stepwise approach was used to assess the statistical significance of relevant covariates.

Model evaluation

Diagnostic plots, parameter precision, IIV decrease, reduction in the OFV, and shrinkage were evaluated during PopPK model development. Parameter precision for the final model was evaluated using nonparametric bootstrapping (1,000 replicates) to generate 95% confidence intervals for parameter estimates. A prediction-corrected visual predictive check (pcVPC) was performed by simulating 1,000 datasets.[31] The pcVPC and bootstrap analyses were performed using Perl-speaks-NONMEM (PsN, version 4.7).[32]

Dosing simulations

The final PopPK model was used to simulate $C_{ss,max}$ and area under the metoclopramide plasma concentration vs. time curve at steady-state from 0 to 6 hours ($AUC_{ss,0-6h}$) in 2,000 virtual patients (500 virtual patients in each PNA group plotted in **Figures 3 and 4**) following oral dosing regimens used in clinical practice: 0.1 mg/kg every 6 hours and 0.15 mg/kg every 6 hours.[8,21,33] The age of virtual patients was within the range of the observed ages in the studied population. The age groups were selected to match the FDA pediatric age groups.[34] Virtual subjects were generated using the European population in PK-Sim (version 7.0, Open Systems Pharmacology Suite, open-systems-pharmacology.com). To match the PK sampling time points of a previous study,[20] the steady-state concentrations were simulated at 0.5, 1, 2, 4, and 6 hours. Simulated $C_{ss,max}$ values were compared with the reported $C_{ss,max}$ range (26–94 ng/mL) for infants with a 75% reduction in reflux time and a concentration (143 ng/mL) observed in one subject at the time of dystonia.[20,21] $AUC_{ss,0-6h}$ was calculated according to Eq. 4 and compared with previously reported $AUC_{ss,0-6h}$ ranges (115–374 ng*hour/mL) in infants with a 75% reduction in reflux time.[20]

$$\mathrm{AUC}_{\mathrm{ss},0-6\mathrm{h}} = \frac{\mathrm{Dose}}{\mathrm{CL}/F} \quad (4)$$

RESULTS

Patient characteristics

A total of 87 quantifiable PK samples from 50 patients were included in the analysis. There were 20 infants (PNA ≤ 2 years), 9 children (2 years < PNA ≤ 12 years) and 21 adolescents (PNA > 12 years). Among all samples collected, only one had a metoclopramide concentration that was below the limit of quantification and was excluded from the analysis. The median (range) number of samples per patient was 1.5 (1–6). There were 25 patients that contributed more than one PK sample, and for 19 of them PK data were collected following an enteral dose. The median (range) PNA was 8.89 years (0.01–19.13). There were 17 infants ≤ 120 days PNA that contributed 34 PK samples (median [range] per subject of 2 [1–5]). Demographic and clinical variables are summarized in **Table 1**.

A total of 20 patients received an i.v. bolus dose (median [range] dose of 0.1 [0.07–0.2] mg/kg) of metoclopramide, and 2 of them also received i.v. infusions (infusion rate of 0.001 and 0.007 mg/kg/min). In 13 patients, metoclopramide was administered orally (median [range] dose of 0.1 mg/kg [0.04–0.15]). Two patients received metoclopramide by both i.v. and oral routes. Fifteen patients received metoclopramide through all three routes of administration (i.v., oral, and nasogastric/nasojejunal/gastrostomy).

PopPK model development and evaluation

A two-compartment model with first-order absorption from the gastrointestinal tract (no lag time) best characterized the data. Estimation of different K_a or F values according to the route of administration did not improve the data fit (there was no improvement in diagnostic plots, and the change in OFV was not significant). Allometric exponents of 0.75 and 1 were fixed for clearance (CL and Q) and volume of distribution (V_c and V_p) parameters, respectively. The estimation of these exponents did not result in a significant drop of OFV, nor did the estimation result in an improvement in overall data fitting. In addition to CL, estimation of IIV in K_a, V_c, V_p, F, or Q resulted in high ETA-shrinkage (> 90%). Therefore, IIV was only estimated for CL. A proportional error model adequately characterized the residual error.

In the covariate analysis, PNA group (group 1, < 1 month; and group 2, ≥ 1 month) and SCr were statistically significant covariates for CL following the forward inclusion step (change in the OFV was −4.3 and −7.0 for PNA group and

SCr, respectively). The IIV decreased 3.4% and increased 1.3% for PNA group and SCr, respectively. In the backward elimination step, SCr level was the only statistically significant covariate for CL (change in the OFV = −7.0). Nonetheless, a weak covariate effect for the relationship between SCr and CL was observed (the exponent value of the power model (Eq. 2) was estimated to be −0.27 and the inclusion of SCr in the model did not decrease the IIV for CL). In addition, the inclusion of SCr caused model instability. To further evaluate this covariate relationship, the influence of each subject in our dataset on the change in OFV with this covariate was explored. As shown in the **Figure S1,** the covariate relationship was no longer significant after dropping one subject from the dataset. In addition, the covariance step was not successful for the model with SCr as a covariate on CL. Therefore, after accounting for body size using WT, no other covariates were included in the final model.

For the final model, the typical values for the PK parameters were expressed according to the following equations:

$$K_a(\text{hour}^{-1}) = 0.4 \tag{5}$$

$$\text{CL(L/hour)} = 19.6 \times \left(\frac{\text{WT}}{70}\right)^{0.75} \tag{6}$$

$$V_c(\text{L}) = 42.9 \times \left(\frac{\text{WT}}{70}\right)^{1} \tag{7}$$

$$Q(\text{L/hour}) = 57.1 \times \left(\frac{\text{WT}}{70}\right)^{0.75} \tag{8}$$

$$V_p(\text{L}) = 83.9 \times \left(\frac{\text{WT}}{70}\right)^{1} \tag{9}$$

$$F = 97\% \tag{10}$$

Shrinkage for the IIV on CL and the proportional residual error parameter were 12.4% and 19.2%, respectively. The IIV for other parameters was not retained in the model, due to high shrinkage values. The population estimates for all parameters are shown in **Table 2**. Standard diagnostic plots for the final model are shown in **Figure 1**.

A pcVPC for all data included in the analysis is shown in **Figure 2**. A total of 6.9% of observed concentrations were outside the pcVPC 90% prediction interval, confirming the good predictive performance of the final model and a slight overestimation of the variability. The parameter estimates of the final PopPK model differed by < 10% from the median bootstrap analysis estimates (**Table 2**).

Dose-response simulation results

An oral dose of 0.1 mg/kg every 6 hours of metoclopramide resulted in 84.3% of virtual patients within the previously reported $C_{ss,max}$ and in 75.5% within $AUC_{ss,0-6h}$ ranges associated with a 75% reduction in reflux time in infants (**Figures 3a and 4a**). Simulated $C_{ss,max}$ levels > 143 ng/mL were seen in 1% of virtual adolescents (12–18 years), and even fewer in patients < 12 years old. An oral dose of 0.1 mg/kg metoclopramide resulted in 87.8% and 82.6% of virtual infants (1 month to 2 years old) having $C_{ss,max}$ and $AUC_{ss,0-6h}$ within the previously reported ranges. Slightly lower $C_{ss,max}$ and $AUC_{ss,0-6h}$ were predicted in neonates < 1 month old (**Figures 3a and 4a**). An oral dose of 0.15 mg/kg every 6 hours resulted 94.2% and 81.8% of virtual patients with the age of < 1 month having $C_{ss,max}$ and $AUC_{ss,0-6h}$ within the previously reported ranges (**Figures 3b and 4b**).

DISCUSSION

In this study, a PopPK analysis for metoclopramide was performed using opportunistic pediatric data. Similar to a previous study, which was the only published metoclopramide PK analysis using a population approach in 47 patients 10–80 years old,[17] a two-compartment model best characterized the data in infants, children, and adolescents. The population estimate for CL was 19.6 L/hour/70 kg, which was comparable to the reported values (20 L/hour/70 kg) in patients with cancer.[17] The population

Table 2 Metoclopramide PopPK parameter estimates for the final model

	Final model		Bootstrap (n = 1,000)[a]		
Parameter	**Estimate**	**RSE (%)**	**2.5th percentile**	**Median**	**97.5th percentile**
K_a, hour^{-1}	0.4	20.4	0.2	0.4	0.8
CL, L/hour/70 kg	19.6	9.6	12.5	18.6	21.8
V_c, L/70 kg	42.9	25.2	4.0	40.7	111.8
V_p, L/70 kg	83.9	12.6	41.6	82.4	275.8
Q, L/hour/70 kg	57.1	24.0	11.5	54.8	238.0
F	0.97	12.5	0.6	0.9	1.0
IIV, CL, %CV	42.4	13.8	25.7	42.2	57.4
Proportional error, %	33.3	21.8	23.6	31.8	39.7

CL, central compartment clearance; %CV, percentage of coefficient of variation; F, bioavailability; IIV, interindividual variability; K_a, first-order absorption rate constant; PopPK, population pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; V_c, central volume of distribution; V_p, peripheral volume of distribution.

[a]Altogether, 19 runs with minimization terminated were skipped when the bootstrap results were calculated; 371 runs with estimates near a boundary were skipped when the bootstrap results were calculated.

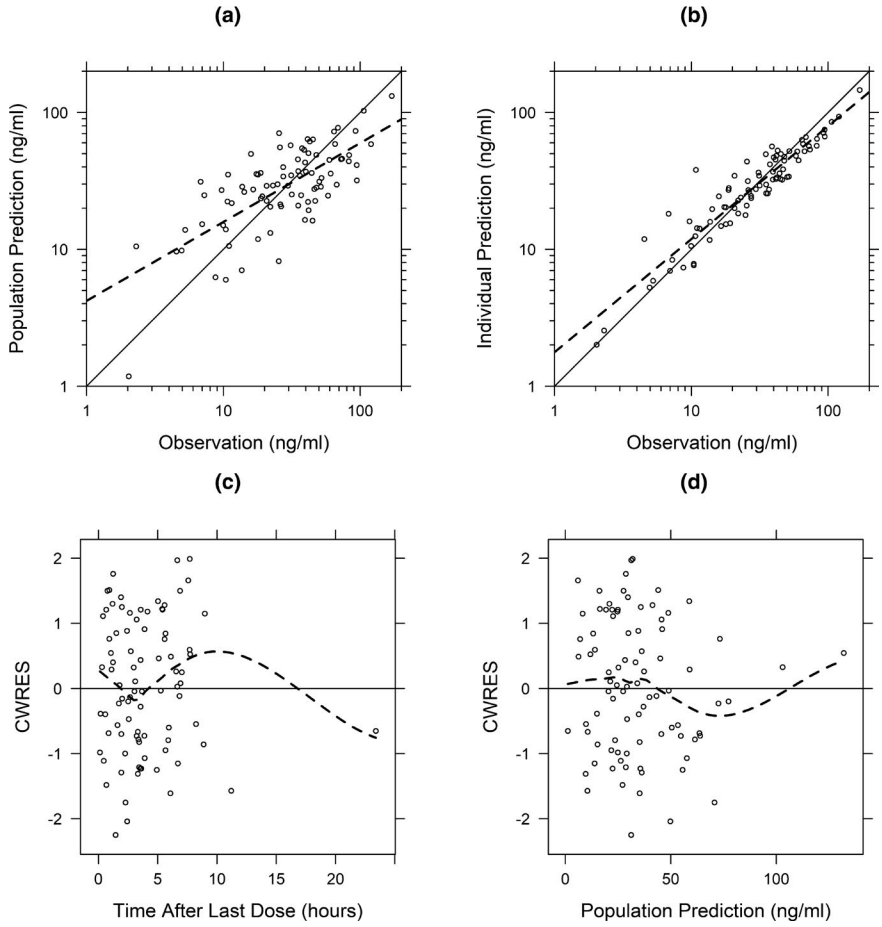

Figure 1 Metoclopramide diagnostic plots for the final population pharmacokinetic model. (**a**) Observed vs. population predictions; (**b**) observed vs. individual predictions; (**c**) conditional weighted residuals vs. time; (**d**) conditional weighted residuals vs. population predictions. The dashed lines represent the linear regression lines in **a** and **b** or loess curves in **c** and **d**. The solid lines represent the lines of unity in **a** and **b** or a conditional weighted residual value of 0 in **c** and **d**. CWRES, conditional weighted residuals.

estimate for steady-state volume of distribution (1.81 L/kg) was comparable to the mean value reported in healthy men (2.22 L/kg), which was calculated using a similar approach ($V_{ss} = V_c + V_p$).[12] However, higher mean values were reported in other studies for various types of volume of distribution (e.g., the terminal phase volume of distribution: 3.4–4.9 L/kg; V_c: ~ 3 L/kg; V_{ss}: ~ 6.9 L/kg).[8,11,18,20,21] The differences in demographic characteristics and disease status (e.g., renal dysfunction) may explain the variations in PK parameters reported in different studies. For instance, one PK study was performed in infants (1–5.5 months) with GER,[20] whereas another analysis was conducted in children (7–14 years) receiving cytotoxic therapy.[21]

The population estimate for bioavailability in our study was 97%, which was higher than previously reported bioavailability of tablets and solutions in adults in some studies (the mean oral bioavailability ranged between 61% and 87%).[11,13] Metoclopramide was administered by four different extravascular routes (oral, nasogastric, nasojejunal, and gastrostomy) in this study, which could at least partially explain the difference in our bioavailability estimate relative to previous studies in adults. Attempts were made to estimate different population values for K_a or F by route of administration; however, inclusion of these parameters did not significantly decrease the OFV or improve model fit. This might be attributable to the limited data available for nasogastric, nasojejunal, and gastrostomy administration.

SCr was found to be a statistically significant covariate for CL, but it was not included in our final model because the inclusion of SCr in the PopPK model resulted in model instability, and the IIV in CL was not reduced with this covariate. We found that this covariate relationship was no longer significant if we removed one subject with a very high SCr level (4.3 mg/dL). In addition, SCr levels were only available for 31 subjects (62%), and missing data could result in bias in the covariate analysis. A previous study reported that the CL of metoclopramide in subjects with renal failure is about 30% of healthy subjects.[14] Considering that metoclopramide and its conjugated metabolites are excreted by the kidneys, it is possible that the SCr level may be a relevant covariate for CL, and we were unable to characterize this relationship due to the limited number of subjects with renal dysfunction in our dataset. Age group (group 1, PNA < 1 month; and group 2, PNA ≥ 1 month) was also a statistically significant covariate for CL in the forward selection step. A lower CL (30% lower) was estimated for subjects with PNA < 1 month in the

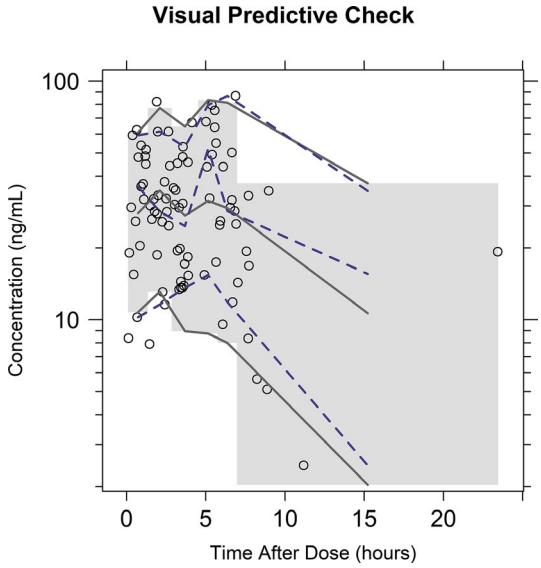

Figure 2 Prediction-corrected visual predictive check of metoclopramide concentrations vs. time with a log-transformed y-axis. The shaded region denotes the 90% prediction interval of the predicted concentrations. The dashed line represents the 5th, 50th, and 95th percentiles for the observed data. The solid line represents the 5th, 50th, and 95th percentiles for the simulated data. Open circles are the observed values.

covariate model with age group. Nevertheless, age group was not retained in the final model during the backward elimination step, suggesting a weak covariate effect. The ontogeny of renal function and metabolizing enzymes (i.e., CYP2D6, UDP-glucuronosyltransferase, and sulfotransferase) may explain part of the IIV in metoclopramide CL in the pediatric population. Although age covariates (PNA, PMA, and GA) did not meet the criteria for inclusion in our PopPK model after accounting for body size differences, this could be attributable to the limited number of infant subjects and sparse sampling.

For simulation studies, we evaluated commonly used dosing of metoclopramide in clinical practice (0.1 and 0.15 mg/kg every 6 hours), given the limited data available regarding the concentration-effect relationships and the efficacy/safety concerns for this drug. The $C_{ss,max}$ and $AUC_{ss,0-6h}$ targets selected for our simulations were also based on limited data. The reported maximum concentration (C_{max}) and area under the concentration vs. time curve from zero to infinity ($AUC_{0-\infty}$) in healthy volunteers were 44 ± 15 ng/mL and 313 ± 113 ng*hour/mL (mean ± standard deviation), respectively, following a 20 mg oral dose (recommended in the product label as a single dose if GER symptoms only occur intermittently), which are generally within the range of the exposure targets we used in our analysis.[4] Our simulation results suggested that a higher dose (i.e., 0.15 mg/kg) might be required for children younger than 2 years to achieve the reported exposure ranges for the treatment of GER. This was consistent with a previously suggested oral dose of 0.15 mg/kg every 6 hours for neonates.[8] Increased CL and volume of distribution values (mean [range] CL: 0.80 L/hour/kg [0.15–2.43]; mean [range] volume of distribution: 6.94 L/kg [4.70–10.54]) were reported in preterm neonates and infants, which could account for the lower drug exposure in this population,[8] yet caution should be taken to dose metoclopramide in infants where the risk of side effects (e.g., tardive dyskinesia and other extrapyramidal symptoms) is higher.[4] Additionally, age was not included in our model as a covariate for CL according to our statistical criteria. Perhaps if we had more rich data for a younger population (i.e., infants and neonates), we might be able to explain the impact of age on CL. Consequently, our results should be interpreted with caution because lower exposure in a younger population might be the result of not including age as a covariate.

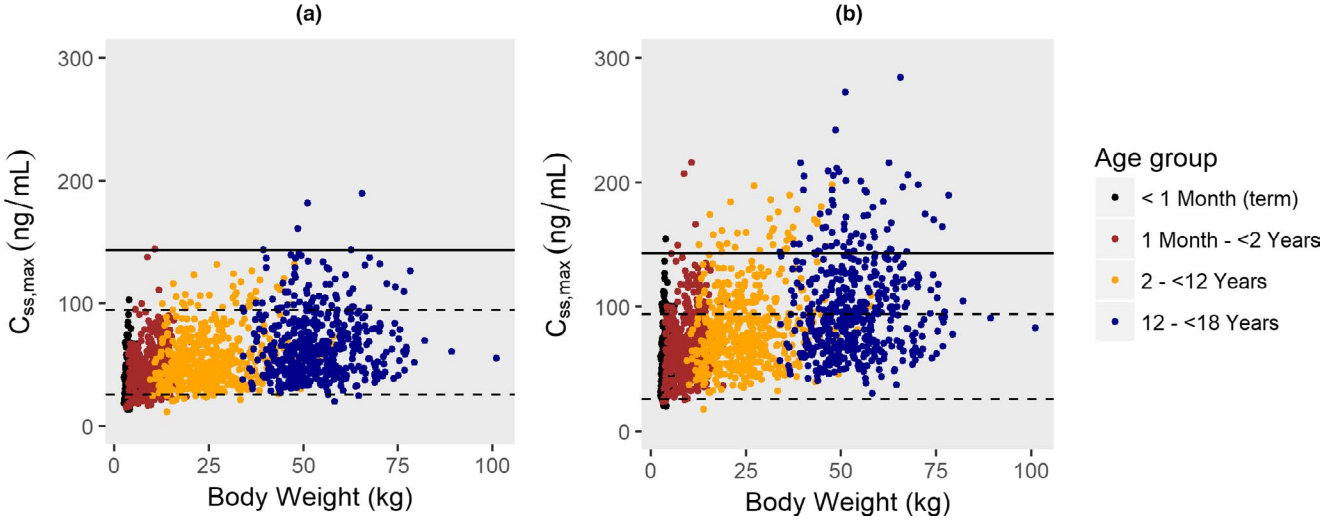

Figure 3 Simulated steady-state maximum concentrations ($C_{ss,max}$) vs. body weight for various pediatric age groups (term infants to adolescents) following oral dosing of 0.1 mg/kg every 6 hours (**a**) and 0.15 mg/kg every 6 hours (**b**). Dashed line: Reported metoclopramide $C_{ss,max}$ range (26–94 ng/mL) in infants with a 75% reduction in reflux time.[20] Solid line: Reported metoclopramide concentration (143 ng/mL) in one child at the time of dystonia.[21]

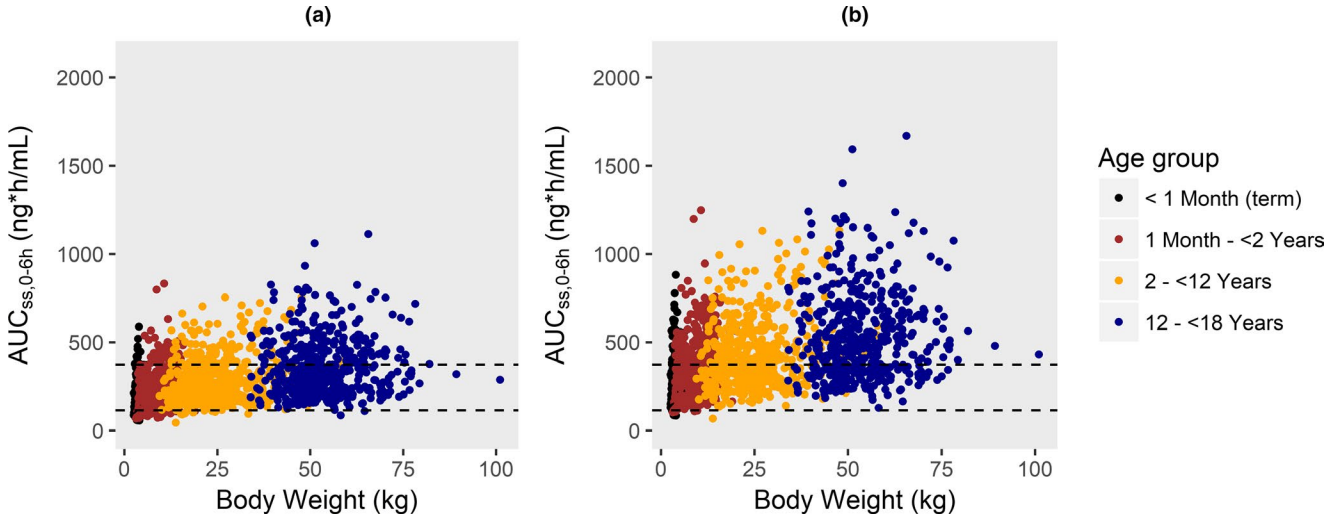

Figure 4 Simulated steady-state area under the metoclopramide concentration vs. time curve from 0 to 6 hours ($AUC_{ss,0–6h}$) for various pediatric age groups (term infants to adolescents) following oral dosing of 0.1 mg/kg every 6 hours (**a**) and 0.15 mg/kg every 6 hours (**b**). Dashed line: Reported metoclopramide AUC range (115–374 ng*hour/mL) in infants with a 75% reduction in reflux time.[20]

Although our study includes the first PopPK model of metoclopramide in children < 10 years of age, it has several notable limitations. First, due to sparse sampling, which is common in PK studies of pediatric populations, limited PK data were available for the analysis. This may explain why the estimation of IIV for parameters other than CL led to high ETA-shrinkage values. Without IIV for V_c and K_a, the individual $C_{ss,max}$ may not be accurately estimated. Although pcVPCs could not be stratified by route of administration due to the limited data, conditional weighted residual plots stratified by i.v. and enteral routes were provided in the **Supplementary Materials** (**Figure S2**), and no bias was observed. In addition, limited PK data may reduce the power to detect clinically relevant covariates, including the impact of age on CL. Second, covariate information was limited in the dataset (e.g., some covariate values were missing, CYP2D6 genotype information was not available, and the number of subjects with renal dysfunction was limited), which may have impacted our ability to detect other significant covariate relationships. Furthermore, this could have contributed to bias in the plasma concentration predictions (e.g., some underprediction for higher concentrations; **Figure 1**). Third, due to the lack of a well-established dose-response relationship for metoclopramide, the efficacy and safety targets we used to interpret our simulation results were based on limited data. Despite these limitations, potential bias exists in the selection of participants enrolled in the study. Because dosage and treatment duration may be dependent upon patient response, participants with lower tolerance and/or a lack of response to metoclopramide might not have been included in the study. Last, external evaluation of the current model using an independent data set could be helpful in determining its potential impact on guiding metoclopramide treatment in children.

In conclusion, a PopPK model was developed to characterize the PKs of metoclopramide in the pediatric population. Simulated $C_{ss,max}$ and $AUC_{ss,0–6h}$ values for an oral dose of 0.1 mg/kg every 6 hours were within the previously suggested range for the majority of virtual subjects, suggesting the appropriateness of the commonly used dose regimen for metoclopramide in the pediatric population for the treatment of GER. Slightly lower $C_{ss,max}$ and $AUC_{ss,0–6h}$ values were predicted for subjects younger than 2 years. When the dose-response relationship of metoclopramide is further elucidated in future studies, our model could be used to evaluate dose regimens and potential adverse effects for pediatric populations.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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Data Sharing Statement. To help expand the knowledge base for pediatric medicine, the Pediatric Trials Network is pleased to share data from its completed and published studies with interested investigators. For requests, please contact: PTN-Program-Manager@dm.duke.edu.

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