Pharmacokinetics of Metoclopramide in Neonates

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Despite its wide use as a prokinetic agent in neonates and infants with gastroesophageal reflux (GER), the pharmacokinetics of metoclopramide have not been characterized in this pediatric subpopulation. A single-dose pharmacokinetic study of oral metoclopramide (0.1 to 0.15 mg/kg) was performed in 10 fasted premature infants (weight 1.1 to 3.2 kg) ranging from 31 to 40 weeks postconceptional age. Metoclopramide was quantitated from repeated blood samples (n = 9 over 24 hours) by high-performance liquid chromatography. A one-compartment open model with first-order absorption best described the plasma concentration-time data. No correlations were observed between gestational, postnatal, or postconceptional age and any of the pharmacokinetic parameters studied. Comparison of the pharmacokinetic parameters from the study cohort and those reported previously from a similar study of older infants revealed no statistically significant differences. However, a prolonged apparent plasma clearance (Cl/F) of metoclopramide was observed in 30% of the infants studied, and the mean Cl/F and apparent steady-state volume of distribution (Vd/F) were approximately 1.4- and 2.1-fold higher, respectively, than values reported in previous studies of metoclopramide disposition in adults. These data suggest that metoclopramide pharmacokinetics may exhibit a developmental dependency. Thus, a metoclopramide dose of 0.15 mg/kg given orally every 6 hours is recommended for the initiation of prokinetic therapy with this agent in infants who are =31 weeks postconceptional age. J Clin Pharmacol 1998;38:122–128.

Gastroesophageal reflux (GER) is common in infants and newborns and is usually treated with thickened feedings, positional therapy, and prokinetic drugs.1–2 Despite the widespread use of prokinetic agents in both neonates and infants, none of these agents are labeled for the treatment of GER within this patient subpopulation. Nonetheless, off-label use of prokinetic agents has become commonplace in neonates and young infants. In many instances, a “patient specific” therapeutic trial of these agents is undertaken in infants with a presumptive diagnosis of GER disease, often made on the basis of clinical evidence of regurgitation associated with feeding. Recently, Pettignano et al3 highlighted the proarrhythmic effects of cisapride in infants and children receiving concomitant therapy with erythromycin, a CYP3A4 inhibitor.4 Clinically important adverse events such as these associated with cisapride have led to a resurgence of interest in the use of metoclopramide for treatment of GER.

Metoclopramide was developed in France as a derivative of orthoprocainamide in the early 1960s, and has been used in the United States for the treatment of GER in infants since the 1980s. Metoclopramide was the first of the benzamides with effects on the...
central nervous system (CNS) and the gastrointestinal tract (e.g., increasing lower esophageal sphincter pressure and improving gastroduodenal coordination), both of which are believed to be caused by modulation of acetylcholine and serotonin.\(^5,^6\) The pharmacokinetics and pharmacodynamics of metoclopramide have been examined in children\(^7\) and infants.\(^8\) However, only the pharmacodynamics of this drug have been evaluated to date in preterm infants.\(^9\)

In view of the extensive hepatic metabolism of metoclopramide both via N-4-sulfate and N-glucuronide conjugation\(^5\) and the ontogeny of phase II enzymes in humans,\(^4\) developmental changes in the disposition of metoclopramide would be anticipated. Given the fact that as many as 50% of patients receiving metoclopramide may experience CNS-related adverse effects,\(^5,^7\) it is reasonable to consider the potential impact of factors such as development on the disposition of metoclopramide and in turn, the dose versus concentration versus effect relationship. We therefore studied the pharmacokinetics of metoclopramide in preterm infants.

### PATIENTS AND METHODS

#### Patients

Ten preterm infants (9 boys, 1 girl, 31–40 weeks postconceptional age) with a diagnosis of GER made on clinical grounds were entered into this study. All infants had normal values for hemoglobin and hematocrit and normal hepatic and renal function, and none had experienced an episode of clinically significant hypoperfusion requiring fluid and/or pharmacologic resuscitation. The decision to institute metoclopramide therapy was made independent of the study protocol by an attending neonatologist. Informed parental consent was obtained before patient enrollment. The experimental protocol was approved by the Human Research Advisory Committee of the University of Arkansas for Medical Sciences, and subjects were enrolled by informed parental consent.

#### Drug Administration and Sampling

A single oral dose of metoclopramide (0.1 or 0.15 mg/kg) was given as a solution formulation after a 1.5-hour period of fasting via oral syringe or nasogastric tube, followed by 10 mL of distilled water (25°C). Age-appropriate feedings (i.e., age and weight appropriate volumes of either infant formula or breast milk) were re instituted 1.5 hours after the metoclopramide dose.

Repeated blood samples (0.3 mL each) for quantitation of metoclopramide were drawn from indwelling umbilical vein catheters placed before metoclopramide administration for nonstudy related medical care. Sample collection was performed immediately before and 0.5, 1, 2, 3, 6, 12, 18, and 24 hours after the dose. Blood samples were allowed to clot in polyethylene tubes at 25°C for 45 minutes. Serum was separated after centrifugation at 5,000 × g for five minutes and was stored at −70°C until analysis.

### Analytical Methods

Quantitation of metoclopramide from serum was performed using a reverse-phase high-pressure-liquid chromatography (HPLC) method\(^10\) on an automated HPLC system (Waters Corporation, Millford, MA). Briefly, serum samples (150 μL) were combined with 50 μL of 5 N NaOH, 25 μL of internal standard (quinidine), and 3.0 mL of methyl t-butyl ether. After extraction, the organic phase was evaporated under N\(_2\) and was reconstituted with mobile phase (acetate/methanol buffer). Chromatography was carried out using a Resolve CN precolumn (Waters Corporation) and a Phenomenex IB SIL 5CN (240 × 4.6 mm) analytical column (Phenomenex, Torrence, CA). The eluate was monitored at 309 nm and 0.001 AUFS where the retention times for metoclopramide and quinidine were 12.5 and 17 minutes, respectively. The range of linearity for the method was 6.25 to 200 ng/mL, the limit of detection was 3.13 ng/mL, and the coefficients of variation for intra- and interday reproducibility were consistently < 10% at 10, 50, and 100 ng/mL. All reagents used for the HPLC assay were purchased commercially (Sigma Chemical Company, St. Louis, MO) and were of the highest grade obtainable.

#### Data Analysis

Individual metoclopramide serum concentration data were curve fit using a peeling algorithm,\(^11\) which yielded initial polynomial parameter estimates. Final parameters were generated using a weighted least-squares algorithm\(^12\) with weight set as the reciprocal of the calculated plasma concentration. Compartmental model selection was made using Akaike's Information Criterion,\(^13\) and the coefficients of variation for parameters estimated in the model. The apparent first-order elimination rate constant was then determined from the best fit of a given data set. The area under the plasma concentration–time curve (AUC) was generated using the linear trapezoidal rule, which was extrapolated to infinity using the final plasma concentration calculated from the curve fit. The apparent total plasma clearance (Cl/F) and
apparent steady-state volume of distribution (Vdss/F) were calculated using a noncompartmental approach, as previously described. Relationships between apparent plasma clearance (Cl/F) and steady-state volume of distribution (Vdss/F) and postnatal and postconceptional age were evaluated using nonlinear regression analysis. Comparison of pharmacokinetic parameters between the present and previous study was undertaken using a two-tailed, unpaired Student t test. All data analyses were accomplished using software packages (Siphar/Base, version 4.0, and S-Stat) available from SIMED (Creteil-Cedex, France). The level of significance accepted for all analyses was α = 0.05.

Additionally, comparison of data for both Cl/F and Vdss/F between this study and a previous study of metoclopramide pharmacokinetics in infants was performed. For reference and comparison purposes, pharmacokinetic parameters from selected pharmacokinetic studies of intravenous metoclopramide in adult subjects were also examined in comparison to the experimental data from our study population.

Throughout the manuscript, descriptive demographic and pharmacokinetic data are presented as the mean ± 1 standard deviation of the mean and the range unless otherwise denoted.

RESULTS

Nine boys and one girl ranging from 31 to 40 weeks postconceptional age (35.3 ± 2.7 weeks) were studied. The subjects ranged in gestational age from 26 to 36 weeks (31.2 ± 3.2 weeks), in postnatal age from 1 to 7 weeks (4.1 ± 1.9 weeks), and in weight from 1.14 to 3.20 kg (1.87 ± 0.57 kg). Five infants were black and five were white. All infants were prescribed metoclopramide before entry into the study for symptomatic treatment of excessive regurgitation associated with feeding. The demographic data for the studied infants are presented in Table I.

Metoclopramide could be quantitated in postdose serum samples in all subjects through 3 hours. Additionally, the drug was measurable in 9 of 10 infants at 6 hours, in 6 of 10 at 12 hours, in 4 of 10 at 18 hours, and in 2 of 10 at 24 hours after drug administration. Of the two subjects with quantifiable concentrations at 24 hours, one (patient 5) had a metoclopramide concentration of 15.5 ng/mL at 24 hours and the other (patient 6) a concentration of 2.5 ng/mL. The mean (± SEM) serum concentration–time data for the study population are illustrated in Figure 1. The apparent peak concentration of metoclopramide in plasma (Cmax = 17.7 ± 6.2, range 8.9–29.2 ng/mL) and the apparent time of peak serum concentration (tmax = 2.5 ± 0.7, range 0.5–4 hrs) were not found to correlate with gestational age, postnatal age, or postconceptional age.

Curve fitting of both individual and mean serum concentration–time data revealed that a one-compartment open model with first-order absorption best described metoclopramide disposition over the 24-hour postdose sampling period. One neonate (patient 9) had metoclopramide serum concentrations below the limit of quantification in the 12- through 24-hour postdose sampling interval; thus accurate estimation of the apparent terminal elimination rate constant and other pharmacokinetic parameters was not possible.

The pharmacokinetic parameters for each infant are presented and summarized in Table II. To examine the potential influence of development on metoclopramide disposition in our study cohort, correlations between age (i.e., gestational age, postnatal age, and postconceptional age) and the elimination rate constant, Cl/F, and Vdss/F were performed. All of these evaluations failed to reveal any statistically significant correlation (linear or nonlinear).

Comparison of data for both Cl/F and Vdss/F between this study and a previous study of metoclopramide pharmacokinetics in infants together with data from previously published pharmacokinetic studies of intravenous metoclopramide are summarized in Table III. In this comparison, the mean values for Cl/F and Vdss/F of metoclopramide in preterm infants were not significantly different from those reported in a previous study of six infants from 1.0 to 5.5 months of age. However, they were approximately 1.4 (for Cl/F) and 2.1 (for Vdss/F) fold higher than reported in previous studies of adults.

DISCUSSION

Gastroesophageal reflux is a common disorder in infants younger than 6 months of age. Symptomatic improvement of this disorder after treatment with metoclopramide has been reported with intravenous doses ranging from 0.1 mg/kg/day in neonates to 0.3 mg/kg intramuscularly per dose in infants. Several subsequent studies have reported beneficial clinical and pharmacodynamic effects of oral metoclopramide in infants with GER without gastroparesis and feeding intolerance. In contrast, other investigations have failed to demonstrate the efficacy of metoclopramide in the treatment of GER in infants with oral doses ranging from 0.5 to 0.6 mg/kg/day.

Hyams et al have suggested that escalation of the metoclopramide dose to 0.3 mg/kg per dose (i.e., 0.9 to 1.2 mg/kg/day) may be required for demonstrable effects on esophageal acid clearance in infants with GER; thereby implying a concentration–effect rela-
Figure 1. Mean ± SEM metoclopramide plasma concentration-time data in nine preterm infants after administration of a single oral dose of metoclopramide solution.
**TABLE II**

Pharmacokinetic Parameters of Metoclopramide in Neonates*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Dose (µg/kg)</th>
<th>Ke (1/hr)</th>
<th>Ka (1/hr)</th>
<th>AUCcorr (ng/mL·hr)</th>
<th>Cmax (ng/mL)</th>
<th>tmax (hrs)</th>
<th>CI/F (L/hr/kg)</th>
<th>Vdss/F (L/kg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>0.157</td>
<td>0.489</td>
<td>258.83</td>
<td>16</td>
<td>3</td>
<td>0.386</td>
<td>5.31</td>
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<td>2</td>
<td>100</td>
<td>0.247</td>
<td>1.72</td>
<td>100.29</td>
<td>20</td>
<td>1</td>
<td>0.997</td>
<td>4.70</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>0.062</td>
<td>1.40</td>
<td>225.54</td>
<td>12</td>
<td>2</td>
<td>0.443</td>
<td>7.53</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>0.065</td>
<td>0.63</td>
<td>321.96</td>
<td>16</td>
<td>3</td>
<td>0.310</td>
<td>5.11</td>
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<tr>
<td>5</td>
<td>150</td>
<td>0.030</td>
<td>1.08</td>
<td>647.63</td>
<td>29.2</td>
<td>4</td>
<td>0.154</td>
<td>5.14</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>0.074</td>
<td>1.61</td>
<td>163.15</td>
<td>13.7</td>
<td>2</td>
<td>0.612</td>
<td>9.38</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>0.222</td>
<td>ND</td>
<td>101.33</td>
<td>25.9</td>
<td>0.5</td>
<td>0.986</td>
<td>4.95</td>
</tr>
<tr>
<td>8</td>
<td>150</td>
<td>0.221</td>
<td>0.257</td>
<td>41.130</td>
<td>8.9</td>
<td>3</td>
<td>2.43</td>
<td>10.54</td>
</tr>
<tr>
<td>9</td>
<td>150</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>150</td>
<td>0.082</td>
<td>7.70</td>
<td>119.37</td>
<td>15.4</td>
<td>3</td>
<td>0.84</td>
<td>9.78</td>
</tr>
</tbody>
</table>

* The elimination and absorption half-life for metoclopramide determined from the mean values of Ke and Ka were 5.4 and 0.37 hours, respectively.

Ke, apparent elimination rate constant; Ka, apparent absorption rate constant; AUCcorr, area under the serum concentration–time curve corrected for a metoclopramide dose of 100 µg/kg; Cmax, apparent peak serum concentration; tmax, time of Cmax; CI/F, apparent total serum clearance uncorrected for extent of absorption; Vdss/F, apparent steady-state volume of distribution uncorrected for absorption; ND, not determined due to insufficient points on the absorption phase (patient 7) or insufficient serum concentration observations to accurately characterize the elimination phase (patient 9).

To illustrate the potential importance of an increased elimination half-life for metoclopramide in neonates, we used a simple one-compartment open model with first-order absorption and average pharmacokinetic parameters from our entire study population (e.g., Ke, Ka, and Vdss/F) as well as a fixed estimate of elimination half-life (i.e., 11 hours) to simulate steady-state peak (Cmax) and trough (Cmin) metoclopramide plasma concentrations for two common oral dosage regimens. As illustrated by the simulated plasma concentrations (Table IV),

older cohort of infants studied previously failed to demonstrate statistically significant differences for either of these pharmacokinetic parameters, the values for Cl/F and Vdss/F in the preterm infants (Table III) were significantly greater than values reported for these parameters in previous studies in adults. Despite the absence of a correlation between metoclopramide pharmacokinetic parameters and age in our study cohort, it is important to note that 3 of the 10 infants studied had an elimination half-life of more than 10 hours (range 10.5–23.1 hrs).

**TABLE III**

Age-Specific Comparison of Metoclopramide Pharmacokinetics

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Population</th>
<th>Route of Administration</th>
<th>CI/F (L/hr/kg)</th>
<th>Vdss (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns et al 1997 (4)</td>
<td>neonates</td>
<td>oral</td>
<td>0.79 ± 0.68</td>
<td>6.94 ± 2.39</td>
</tr>
<tr>
<td>Kearns et al 1988 (8)</td>
<td>infants</td>
<td>oral</td>
<td>0.66 ± 0.39</td>
<td>4.94 ± 1.06</td>
</tr>
<tr>
<td>Ross-Lee et al 1981 (15)*</td>
<td>adults</td>
<td>intravenous</td>
<td>0.53 ± 0.19</td>
<td>3.43 ± 1.18</td>
</tr>
<tr>
<td>Block et al 1981 (16)*</td>
<td>adults</td>
<td>intravenous</td>
<td>0.55 ± 0.12</td>
<td>3.10 ± 0.64</td>
</tr>
</tbody>
</table>

* Data from Ross-Lee et al reflects a 10-mg metoclopramide dose, while that from Block et al reflects a 20 mg-dose.

Data are presented as mean ± standard deviation. Comparison of both CI/F and Vdss/F between neonatal and infant studies revealed P > 0.05 (P = 0.25 for CI/F and 0.07 for Vdss/F). CI/F, apparent total serum clearance uncorrected for extent of absorption; Vdss/F, apparent steady-state volume of distribution uncorrected for absorption.
the consequence of administering “standard” metoclopramide doses (i.e., 0.2 mg/kg every 6 hours) to an infant with a prolonged elimination half-life are almost two- and three-fold increases in $C_{\text{max}}$ and $C_{\text{min}}$, respectively, and an approximate two-fold increase in the AUC for a 6-hour dosing interval. Although not specifically evaluable from the data collected in this study or from previous pediatric investigations of metoclopramide reported in the literature, it appears reasonable to speculate that in those preterm neonates with prolonged plasma clearance, “standard” doses of the drug could easily result in the accumulation of steady-state serum concentrations, which could possibly produce toxicity.

Although the seemingly increased apparent volume of distribution for metoclopramide in our preterm infants might be explained in part by the physicochemical characteristics of the drug and known developmental changes in body composition, the same is not true for the findings relative to plasma clearance (Table III). It is possible that “enhanced” plasma clearance of metoclopramide in some neonates and in infants may represent developmental variations in isoform-specific sulfotransferase activity responsible for the N-4-sulfation of metoclopramide; a pathway responsible for a major portion (32%) of the drug’s metabolism in humans. This phenomenon (enhanced sulfation) has been previously described for aceterminophen metabolism in infants and demonstrates the potential importance of developmental differences in the ontogeny of phase II enzymes.

In contrast, the apparent delayed plasma clearance in 30% of our preterm infants, which did not appear to be associated with age (Table II), may not represent deficient sulfotransferase activity associated with immaturity but rather normal pharmacogenetic variability (e.g., a poor-metabolizer phenotype) for sulfotransferase isoforms, as has recently been reported by Weinshilboum et al. As illustrated by our pharmacokinetic simulations (Table IV), the administration of repeated doses of metoclopramide previously recommended for the management of GER in these neonates could easily result in metoclopramide plasma concentrations capable of increasing the risk of adverse drug effects. Thus, the pharmacokinetic data from our study cohort (Table II) and the aforementioned simulations (Table IV) would appear to support the initiation of metoclopramide therapy in the neonate who is >31 weeks postconceptional age with an oral dose of 0.15 mg/kg given every 6 hours.

Metoclopramide use in the management of GER and feeding intolerance in neonates remains a common clinical practice in the United States and Europe. The data from this investigation demonstrate the potential for developmental dependence, and perhaps normal heterogeneity in the biotransformation of metoclopramide, to have a sufficient impact on the pharmacokinetics of this drug to alter the dose—concentration—effect relationship. Until future studies are available to more clearly define the pharmacokinetic—pharmacodynamic interface for metoclopramide in both preterm and term neonates, attention to the potential impact of ontogeny on the drug’s disposition should be considered in the decision to prescribe therapy in this pediatric subpopulation and in monitoring these patients for metoclopramide-associated adverse effects.

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