Doxylamine Pharmacokinetics Following Single Dose Oral Administration in Children Ages 2–17 Years

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Abstract
To characterize doxylamine pharmacokinetics in children. This study was conducted in 41 subjects, ages 2–17 years. Doxylamine succinate doses based on age/weight ranged from 3.125 to 12.5 mg. A single oral dose was administered with 2 to 4 oz. of water or decaffeinated beverages 2 hours after a light breakfast. Plasma samples were obtained before and for 72 hours after dosing and analyzed for doxylamine using HPLC MS/MS. Pharmacokinetic parameters were estimated using non-compartmental methods and relationships with age were assessed using linear regression. Over the fourfold dose range, Cmax was similar while AUC increased only 60%, although not statistically significant (P-value = 0.0517). As expected due to increasing body size, CLo and Vz/F increased with age. Due to a similar increase with age for CLo and Vz/F, no age-related differences in t1/2,z were observed (~16 hours). Overall, the single doses were well tolerated. Somnolence was the most common reported AE with no apparent differences in incidence noted with age. An age/weight dosing nomogram utilizing a fourfold range of doses achieves similar Cmax, whereas AUC increases only 60%.

Keywords
doxylamine, pharmacokinetics, pediatrics, over-the-counter (OTC)

Doxylamine succinate, a member of the ethanolamine H1 blockers, is an antihistamine in over-the-counter (OTC) cough and cold medicines. It has been administered alone, or in combination with other active ingredients approved for human use since 1948, initially as an antihistamine and more recently in non-prescription sleep aids and in cough/cold products.1,2 It has also been used in combination with pyridoxine for the treatment of morning sickness in pregnant women. Although withdrawn from the market in the 1980s, it has recently been reapproved by FDA.

Doxylamine pharmacokinetics have been described in adults following single and multiple dosing. Following single dose oral administration of 25 mg doxylamine succinate, pharmacokinetic parameters included a Cmax of ~100 ng/mL generally occurring between 2 and 3 hours, a CLo of ~180 mL/h/kg, a CLR of ~100 mL/h/kg, and a t1/2,z of 10 hours.3,4 CLo was reduced in older men compared to younger men with no age effects in women. Upon multiple dosing of 12.5 mg every 6 hours, steady state was achieved within 1 week.5 Estimated pharmacokinetic parameters included CLo and CLR of 150 and 110 mL/h/kg, respectively, and a t1/2,z of ~14 hours.

Doxylamine metabolism has not been extensively characterized. One report provided a limited assessment in one male and one female volunteer.6 Based on urinary data, doxylamine undergoes N-dealkylation to N-desmethyl and N,N-didesmethyldoxylamine, with subsequent N-acetyl conjugation.

Historically, dosing in pediatric patients has been empirically based on body weight and/or age since pharmacokinetics and pharmacodynamics data have generally been unavailable. Current OTC monograph labeling for cold, cough, allergy, bronchodilator, and antiasthmatic drugs, indicates children 12 years and above be administered the adult dose and children 6–<12 years of age be administered 1/2 the adult dose. For children <6 years of age, a physician should be consulted.7 More recently, the use of doxylamine in children <4 years of age is not recommended.

The primary purpose of this study was to determine if an age/weight based dosing nomogram for doxylamine succinate achieves similar systemic exposure (Cmax and AUC) over the range of 2–17 years of age. In addition, relationships between doxylamine pharmacokinetic parameters (CLo, Vz/F, and t1/2,z) and age were assessed.
Methods

Study Design
This was a single-dose, open-label multicenter study. The study population consisted of non-smoking, healthy children, ages 2–17 years with a minimum weight of 24 pounds and a body weight greater than the 5th and less than the 95th percentile for weight, based on age and sex. Subjects had a history of allergic rhinitis, or a history of frequent upper respiratory infections, and in the opinion of the Investigator, may have benefited from use of an antihistamine. Exclusion criteria included febrile illness greater than 100°F within 7 days prior to dosing and reported use of non-prescription drug or supplemental vitamin usage within 5 days, prescription drug or herbal remedy usage within 14 days, and enzyme-inducer, enzyme-inhibitor, or reported chronic exposure to enzyme-inducers (such as drugs, paint solvents, or pesticides) within 30 days prior to dosing. Up to 44 children were to be enrolled with the goal of completing 36 children with approximately 2 children at each age.

The study was reviewed and approved by University of Louisville IRB (Louisville, KY), Sterling Institutional Review Board (Atlanta, GA), Compass IRB (Mesa, AZ), and LSUHSC-Shreveport School of Medicine IRB (Shreveport, LA).

Study Conduct
Subjects arrived at the clinical site the night prior to dosing. After midnight, subjects were fasted, but were permitted to eat a light meal (e.g., toast and/or yogurt and clear liquids) 2 hours prior to dosing. Small amounts of water (≤120 mL) were allowed 1 hour prior to dosing. Subjects were permitted to be fed their normal diet (theose containing no more than 100°F within 7 days prior to dosing and reported use of non-prescription drug or supplemental vitamin usage within 5 days, prescription drug or herbal remedy usage within 14 days, and enzyme-inducer, enzyme-inhibitor, or reported chronic exposure to enzyme-inducers (such as drugs, paint solvents, or pesticides) within 30 days prior to dosing. Up to 44 children were to be enrolled with the goal of completing 36 children with approximately 2 children at each age.

The study was reviewed and approved by University of Louisville IRB (Louisville, KY), Sterling Institutional Review Board (Atlanta, GA), Compass IRB (Mesa, AZ), and LSUHSC-Shreveport School of Medicine IRB (Shreveport, LA).

Drug Administration
A single dose of doxylamine succinate solution (12.5 mg/30 mL) based on age/weight was administered by oral syringe as follows:

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Weight Range (lb)</th>
<th>Dose (mL)</th>
<th>Doxylamine Succinate Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 2</td>
<td>Under 24</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
<tr>
<td>2-3</td>
<td>24-35</td>
<td>7.5</td>
<td>3.125</td>
</tr>
<tr>
<td>4-5</td>
<td>36-47</td>
<td>10</td>
<td>4.17</td>
</tr>
<tr>
<td>6-8</td>
<td>48-59</td>
<td>15</td>
<td>6.25</td>
</tr>
<tr>
<td>9-10</td>
<td>60-71</td>
<td>20</td>
<td>8.33</td>
</tr>
<tr>
<td>11</td>
<td>72-95</td>
<td>25</td>
<td>10.42</td>
</tr>
<tr>
<td>12-17</td>
<td>≥95</td>
<td>30</td>
<td>12.5</td>
</tr>
</tbody>
</table>

For older children (e.g., 10 or 11 years) who weighed more than 95 pounds and were <95% percentile for weight based on age and gender, a maximum dose of 10.42 mg doxylamine succinate was administered. All adolescents, ages 12–17 years old were administered 12.5 mg doxylamine succinate regardless of weight.

Subjects drank 60–120 mL of water or decaffeinated beverages (e.g., Sprite® or ginger ale) after swallowing the dose. Subjects were required to swallow the complete dose to continue in the study.

Blood Sampling
Two milliliters of blood was collected prior to and at 1, 2, 4, 6, 8, 10, 14, 24, 36 (±4), 48 (±4), and 72 (±4) hours after dosing. Over the first 24 hours, samples were obtained from an indwelling catheter; subsequent samples were obtained via individual venipunctures. Plasma (potassium EDTA) was harvested and stored at −20°C until assayed.

Safety Monitoring
Safety was evaluated based on clinical observations and assessment of adverse events (AEs), subjective symptoms and complaints via individual interviews, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), physical examination, and pre-dose and post-dose clinical chemistry and hematology, including creatine phosphokinase (CPK). Vital signs were obtained prior to and at 1, 2, 3, 4, 24, and 72 hours after dosing. Additional sedation assessments were evaluated as described in the sedation monitoring section below and are also included as part of the AE counts.

Sedation Monitoring
An assessment of sedation using the University of Michigan Sedation Scale (UMSS) as developed by Malviya8,9 was completed at baseline, every hour for 6 hours following dosing, and subsequently at the discretion of the Investigator. The UMSS is an observational tool for assessing the level of alertness on a 5-category scale as follows:

0 = Awake and alert;
1 = Minimally sedated (subject is tired/sleepy, gives an appropriate response to verbal conversation and/or sounds);
2 = Moderately sedated (subject is somnolent/sleeping but can be easily aroused with light tactile stimulation);
3 = Deeply sedated (arousable only with significant physical stimulation);
4 = Unarousable.

Sample Assay
An HPLC MS/MS method, developed and validated by the Bioanalytical Department at Procter & Gamble,
Mason, OH, was used to analyze doxylamine plasma concentrations. Doxylamine and its stable isotope-labeled internal standard (D<sub>2</sub>-doxylamine) were isolated from human plasma by a protein precipitation procedure using a 96-well format. The analyte and internal standard were subjected to reverse-phase high performance liquid chromatographic (HPLC) analysis on a C18 column (2.1 mm × 50 mm, 2.5 μm particles), then detected and quantified using mass spectrometry operating under multiple reaction monitoring (MRM) conditions. Human plasma calibration standards were used to quantitate human Quality Control (QC) samples and unknown specimens. The nominal range of quantitation used during the study was 0.20–200 ng/mL based on a 0.050 mL aliquot of human plasma. Based on QC samples run during validation (0.6–120 ng/mL), interday variability was 5% or less, and interday accuracy ranged from −4.2% to 0.8%. For QC samples run during the study sample assays, interday variability was 8.4% or less and interday accuracy ranged from −5.0% to −0.8%. During assay development, sample stability was determined to be 103 days; study samples were analyzed within 69 days of sample collection.

**Pharmacokinetic Analysis**

Individual doxylamine plasma concentration–time profiles were analyzed using non-compartmental analysis. The maximum plasma concentration (C<sub>max</sub>) and the time at which the maximum occurred (t<sub>max</sub>) were determined from the individual doxylamine plasma concentration–time profiles. The terminal exponential rate constant (λz) was determined using linear least squares regression of the terminal phase of the log concentration–time profile. The terminal exponential half-life (t<sub>1/2,z</sub>) was obtained as 0.693/λz. Area under the plasma concentration–time curve (AUC<sub>last</sub>) was determined up to the last observed quantifiable concentration, using the linear trapezoidal rule. The extrapolated area under the plasma concentration–time curve (AUC<sub>ext</sub>) was obtained based on the last observed quantifiable plasma concentration and the terminal exponential half-life. Area under the plasma concentration–time profile from time zero to infinity (AUC) was the sum of AUC<sub>last</sub> and AUC<sub>ext</sub>. Oral clearance (CL<sub>o</sub>) and terminal volume of distribution (uncorrected for bioavailability) (V<sub>f</sub>/F) were determined using standard equations. Data analyses were performed using WinNonlin v5.1.1 and SAS v9.1.3.

**Statistical Analysis**

The relationship between various PK parameters (C<sub>max</sub>, AUC, CL<sub>o</sub>, CL<sub>o</sub>/BW, and V<sub>f</sub>/F) and age was assessed using linear regression. In addition, CL<sub>o</sub> and V<sub>f</sub>/F were allometrically scaled based on the approach outlined by Anderson and Holford (i.e., CL<sub>o</sub> /[BW/70 kg]<sup>1/4</sup>) [V<sub>f</sub>/F]/kg). The relationship between allometrically scaled parameters and age were also assessed using linear regression. Least squares estimates of the intercept and slope and their associated standard errors, 95% confidence intervals, and P-values were obtained for each analysis. An age-related change was concluded if the P-value associated with the slope was < .05 for a 2-sided test.

**Results**

**Subjects Demographics**

Forty-one subjects were enrolled with 40 subjects completing the study. One subject was discontinued due to incomplete dosing (age group: 6–11 years). Subject demographics for subjects enrolled in the study are summarized in Table 1. For each age, there was a minimum of two subjects. The majority of subjects were male (N = 25) and of non-Hispanic or Latino ethnicity (N = 33). As expected, body weight increased on average with age.

**Doxylamine Exposure/Pharmacokinetics**

Doxylamine plasma concentration–time profiles following single dose oral administration are illustrated in Figure 1 with corresponding pharmacokinetic parameters summarized in Table 2 by age group (2–5, 6–11, and 12–17 years). The relationship between C<sub>max</sub> and age

<p>| Table 1. Subject Demographics for Pediatric Subjects Administered a Single Oral Dose of Doxylamine |</p>
<table>
<thead>
<tr>
<th>Demographics</th>
<th>2–5 years</th>
<th>6–11 years</th>
<th>12–17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&lt;sup&gt;a&lt;/sup&gt; (year)</td>
<td>Mean 3.6</td>
<td>8.5</td>
<td>14.5</td>
</tr>
<tr>
<td>CV (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.8</td>
<td>17.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Body weight&lt;sup&gt;d&lt;/sup&gt; (kg)</td>
<td>Mean 17.80</td>
<td>31.46</td>
<td>59.91</td>
</tr>
<tr>
<td>CV (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>13.6</td>
<td>25.5</td>
<td>14.8</td>
</tr>
<tr>
<td>Height&lt;sup&gt;e&lt;/sup&gt; (cm)</td>
<td>Mean 105.61</td>
<td>132.47</td>
<td>163.52</td>
</tr>
<tr>
<td>CV (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9.6</td>
<td>7.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Multi-racial</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
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</tr>
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<td>Hispanic or Latino</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>7</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup>Age categories are those listed in the doxylamine monograph.

<sup>b</sup>Age is calculated at screening.

<sup>c</sup>Coefficient of variation.

<sup>d</sup>Weight is obtained at admission.

<sup>e</sup>Height is obtained at screening.
indicated no statistically significant age-related dosing differences using the age/weight based dosing nomogram utilizing a fourfold range of doses (Figure 2, Panel A). Although not statistically significant (P-value = .0517), a small increase in AUC was noted with age (~60% increase from 2 to 17 years based on the regression equation; Figure 2, Panel B). Doxylamine time to peak concentration (Tmax) occurred slightly later in children ≥6 years as compared to children <6 years (2 hours vs. 1 hours) whereas the terminal exponential half-life (t1/2,z) was similar across age groups (14.8–17.5 hours).

The relationship between oral clearance and the terminal volume of distribution with age are shown in Figures 3 and 4, respectively. Observed oral clearance increased with age (Figure 3, Panel A), whereas body weight-adjusted oral clearance decreased with age (Figure 3, Panel B). Over the range of 2–17 years, oral clearance increased ~150% (4.9–12.3 L/h) and body weight adjusted oral clearance decreased ~50% (0.34–0.16 L/h/kg). However, allometrically adjusted oral clearance normalized to 70 kg was not statistically significantly related to age (i.e., P-value = .12; Figure 3, Panel C). The observed terminal volume of distribution, unadjusted for bioavailability, also increased with age (Figure 4, Panel A) where the allometrically adjusted terminal volume of distribution decreased with age (Figure 4, Panel B). Over the range of 2–17 years, the terminal volume of distribution increased ~175% (109–303 L, respectively) and the allometrically adjusted terminal volume of distribution decreased ~50% (7.9–4.0 L/kg, respectively).

**Safety Results**

There were no serious AEs or withdrawals due to AEs during this study. There were a total of 19 mild or moderate AEs experienced by 16 subjects with 6, 4, and 9 AEs reported in the 2–5, 6–11, and 12–17 age groups, respectively. Seventeen (89%) of the AEs were of mild

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**Table 2. Geometric Mean (CV%) Doxylamine Pharmacokinetics Summarized by Age Group Following Single Dose Oral Administration**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>2–5 Age Group (n = 9)</th>
<th>6–11 Age Group (n = 16)</th>
<th>12–17 Age Group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>50.1 (22.5)</td>
<td>65.8 (19.9)</td>
<td>63.2 (42.9)</td>
</tr>
<tr>
<td>tmax(^a) (h)</td>
<td>1.00 (1.00, 2.05)</td>
<td>2.00 (1.00, 4.05)</td>
<td>2.00 (1.00, 2.05)</td>
</tr>
<tr>
<td>AUC (ng h/mL)</td>
<td>461.9 (51.2)</td>
<td>810.1 (27.9)</td>
<td>827.0 (45.4)</td>
</tr>
<tr>
<td>CLo (L/h)</td>
<td>5.89 (55.3)</td>
<td>6.94 (31.5)</td>
<td>10.5 (45.4)</td>
</tr>
<tr>
<td>CLo/BW (L/h/kg)</td>
<td>0.334 (51.4)</td>
<td>0.226 (28.1)</td>
<td>0.177 (42.0)</td>
</tr>
<tr>
<td>CLo allometric (L/h; normalized to 70 kg)</td>
<td>16.55 (51.9)</td>
<td>12.87 (26.5)</td>
<td>11.91 (42.9)</td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>125.7 (45.5)</td>
<td>175.5 (43.3)</td>
<td>235.7 (56.7)</td>
</tr>
<tr>
<td>Vz/F/BW (L/kg)</td>
<td>7.12 (51.6)</td>
<td>5.72 (40.7)</td>
<td>3.97 (56.4)</td>
</tr>
<tr>
<td>t1/2,z (h)</td>
<td>14.8 (55.7)</td>
<td>17.5 (30.5)</td>
<td>15.5 (34.3)</td>
</tr>
</tbody>
</table>

\(^a\)Median (min, max) shown for tmax.
severity and two (11%) were of moderate severity. Seventy-four percent (74%) of all AEs were considered doubtfully related to the study medication. Four (21%) of the AEs (one in the 2–5 years old age group; three in the 12–17 years old age group) were considered to be possibly related to the study medication and only one AE (5% of total AEs), noted in the 12–17 years old age group was considered to be probably drug related.

Sedation or somnolence was the most common AE reported and accounted for 16 of 19 total AEs...
Figure 3. The relationship between doxylamine oral clearance (Clo; Panel A), body weight adjusted oral clearance (Clo/BW; Panel B) or allometrically scale oral clearance (Clo, allometric; Panel C) and age following single dose oral administration.
across 15 subjects; 56% (5/9) of the subjects in the 2–5 years old age group, 18% (3/17) of the subjects in the 6–11 years old age group and 47% (7/15) of the subjects in the 12–17 years old age group. No apparent differences were noted in the incidence of somnolence across age groups. Additional details on these sedation related AEs are provided in the sedation results section.

Three other AEs included one report each of headache, otitis media, and dizziness.

There were no AEs related to laboratory measurements reported in the study and there were no markedly abnormal laboratory values.

**Sedation Results**

A majority of subjects (25/41, 61% of study participants) were awake and alert during the 6-hour period and did not have any level of sedation as assessed by UMSS. There was no obvious trend in the incidence of sedation across different age groups.

Of the 16 subjects who experienced any level of sedation, 75% (12/16) were assessed as minimally sedated only based on UMSS. In all but one of these subjects with minimal sedation, sedation was noted at only one of the 6 hourly assessments and the subjects were awake and alert at all other hourly assessments. The percent of subjects

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**Figure 4.** The relationship between doxylamine terminal volume of distribution (Vz/F; Panel A) or allometrically scaled terminal volume of distribution (Vz/F/BW; Panel B) and age following single dose oral administration.
Discussion

This study characterized the pharmacokinetic parameters of doxylamine administered to children 2–17 years of age following a single oral dose of a doxylamine succinate solution based on age (3.125–12.5 mg).

Following single dose oral administration based on an age/weight nomogram, no statistically significant relationship for \(C_{\text{max}}\) across 2–17 years was observed (i.e., no change in \(C_{\text{max}}\) with age). However, the median time to achieve \(C_{\text{max}}\) appeared to be greater in children 6 years and above (1 hour for 2–<6 years vs. 2 hours for 6 years and above). Over this fourfold range of doses, a small increase (≈60%) in AUC was noted with increasing age, although it did not achieve statistical significance (\(P\)-value = .0517).

As expected due to increasing body size, oral clearance increased significantly (\(P\)-value = .0002) with age (≈150% over the range of 2–17 years). When clearance was body weight adjusted, which is an approach commonly used in many investigations, the relationship with age was still statistically significant and decreased (≈50%). However, using an allometrically scaled approach more recently recommended by Anderson and Holford,12 no statistically significant age-related change in oral clearance was observed. For the terminal volume of distribution, the expected age-related increase was observed (≈175% increase over the range of 2–17 years). However, when the terminal volume of distribution was allometrically scaled, a significant decrease over the age range was observed (≈50%). Although a significant relationship for the terminal volume of distribution following allometric scaling still existed with age, the range of predicted values decreased ≈70% over the range of 2–17 years of age. Since the unadjusted oral clearance and the terminal volume of distribution both showed a similar increase with age, no age-related change in the terminal exponential half-life was observed. Overall, these analyses re-emphasize the importance of allometric scaling for clearance and volume of distribution prior to interpretation of age related (maturation) effects.

When results from this study are compared to those previously reported for adults, good agreement is generally observed. Based on the predicted values within this study for 17-year-old children, \(C_{\text{max}}\) following 12.5 mg (69 ng/mL) is slightly higher than the dose adjusted \(C_{\text{max}}\) observed in adults (25 mg; ≈100 ng/mL). However, in adults the time to achieve \(C_{\text{max}}\) is 2–3 hours whereas the time in children is ≈2 hours. The higher dose adjusted \(C_{\text{max}}\) in children may be due in part to a slightly more rapid absorption based on the earlier \(T_{\text{max}}\) and may possibly reflect differences in formulations between the adult and pediatric studies. For oral clearance, results in children are generally similar to those observed in adults (164 mL/h/kg in 17 years old vs. 180 mL/h/kg in adults). The terminal exponential half-life observed in children appeared to be independent of age (≈16 hours) in the pediatric cohort evaluated in this study. In adults, the reported \(t_{1/2,\text{r}}\) following single dose oral administration is ≈10 hours.3,4 This apparent difference may be related to the duration of sample collection. In the adult single-dose studies, blood samples were obtained over 30 hours whereas in this study, blood sampling occurred over 72 hours. When blood sampling was extended in a multiple dose study conducted in adults (48 hours following the last dose), estimates in the terminal exponential half-life were similar (i.e., 14 hours vs. 16 hours in adults and children, respectively).

Doxylamine was well-tolerated in this study. There were no serious AEs and no withdrawals due to an AE. The most prevalent AEs were sedation and somnolence which did not appear to be age related. Seventy-five percent (75%) of the subjects with sedation were assessed as minimally sedated and only one subject was assessed as deeply sedated. Respiratory depression was not reported in any subject. In addition, no markedly abnormal laboratory values were observed. The incidence of mild sedation being the most common side effect is consistent with the side effect profile of doxylamine in adults1 and is also consistent with doxylamine being indicated as an OTC sleep aid. A conclusive evaluation of the sedation potential of doxylamine in this study population could not be undertaken in the absence of a control group.

In conclusion, the age/weight based dosing nomogram for doxylamine succinate utilizing a fourfold range of doses over the age of 2–17 years of age achieves similar peak plasma concentrations across the pediatric cohort evaluated in this study. Although not statistically significant (\(P\)-value = .0517), a small increase (≈60%) in AUC was noted with increasing age. However, allometric scaling indicates no statistically significant age-related (i.e., maturation) change in oral clearance within this population. All treatments were well-tolerated; the most prevalent AEs were those of sedation and somnolence. There were no serious AEs and no drop-outs due to AEs.

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**Declaration of Conflicting Interests**

GB, GAT, RG, DH, and MS are current or former employees of The Procter & Gamble Company and may have stock and/or stock options. GAT is a paid consultant to The Procter & Gamble Company.

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