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Single-Dose Pharmacokinetic Study of Diphenhydramine HCl in Children and Adolescents

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Abstract

Diphenhydramine pharmacokinetics were characterized following a single oral dose in children aged 2 to 17 years using a weight- and age-based dosing schedule with more tiers than the current age-based dosing schedule recommended by the nonprescription drug monograph. This study was conducted in 42 subjects, aged 2 to 17 years. Doses were based on a weight-age dosing schedule, ranging from 6.25 to 50 mg. An oral dose was administered with water about 2 hours after a light breakfast. Plasma samples were obtained up to 48 hours after dosing and analyzed for diphenhydramine. Pharmacokinetic parameters were estimated using noncompartmental methods, and the relationship of oral clearance with age was assessed using linear regression. Over an 8-fold range of doses, C_{max} and AUC increased ~90 % to ~140% across age groups, with a similar T_{max} (1.5 hours). Oral CL/F increased with age, but after allometric scaling, no maturation-related change in CL/F was apparent. Mild somnolence was the most commonly reported adverse event (95% of the subjects). A weight-age dosing schedule using an 8-fold range of doses achieved C_{max} and AUC that increased about 2-fold across age groups. No effect of maturation on CL/F was observed after allometric scaling.

Keywords

diphenhydramine, pharmacokinetics, pediatric, adolescent, allometric

Diphenhydramine hydrochloride (HCl) is available globally in over-the-counter (OTC) allergy, cough, and cold medicines. It is an ethanolamine and first-generation H_1 antagonist that acts as a reversible, competitive inhibitor of histamine binding to the H_1 receptor.[1] H_1 antagonists, especially ethanolamines, have significant antihistaminic and antimuscarinic activities and concurrent sedative properties. In the United States, diphenhydramine HCl is regulated by an OTC monograph, and is indicated for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes from hay fever or other upper respiratory allergies and for the temporary relief of runny nose and cough that may occur with the common cold.[2]

Diphenhydramine pharmacokinetics in adults have been reported for single doses of 25 and 50 mg diphenhydramine HCl.[3–6] Following intravenous administration of 50 mg, diphenhydramine pharmacokinetic parameters included a total systemic clearance of 6.16 mL/min/kg, a terminal volume of distribution of 4.54 L/kg, and a terminal exponential half-life of 8.5 hours.[5] Following oral administration of 50 mg in two studies, diphenhydramine attained maximum concentrations at 2.3 and 2.2 hours, and had terminal exponential half-lives of 9.2 and 9.8 hours, respectively. In another study conducted in adults following oral administration of 1.25 mg/kg, similar results were observed for systemic exposure parameters (C_{max} and AUC) after adjusting for dose, with maximum concentrations occurring at 1.7 hours, and a terminal exponential half-life of 9.2 hours.[7]

Diphenhydramine undergoes first-pass metabolism after oral administration with an absolute bioavailability of 72% ± 8%, and it is mainly cleared systemically via metabolism, with about 2% of the dose being recovered unchanged in urine.[3,8] Diphenhydramine is primarily metabolized via demethylation to N-demethyl diphenhydramine, which is subsequently

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demethylated to N,N-didemethyl diphenhydramine and further metabolized by oxidative deamination to diphenylmethoxyacetic acid.[3,9,10] Based on a study conducted in adults, the initial N-demethylation does not appear to be related to cytochrome p450 2D6 (CYP2D6) activity, whereas the subsequent N-demethylation appears to be reduced in subjects who were phenotyped as CYP2D6 poor metabolizers.[8] In drug-interaction pharmacokinetic studies with venlafaxine and metoprolol, diphenhydramine was shown to be an inhibitor of CYP2D6 without being extensively metabolized by this cytochrome P450 isozyme.[8,11]

Limited diphenhydramine pharmacokinetics data are available in children. One study of seven children (mean age = 8.9 years) compared the pharmacokinetics following a single oral dose of 1.25 mg/kg with adults.[3] Maximum concentrations occurred slightly earlier (1.3 hours) and the half-life was shorter (5.4 hours), the latter of which may be due in part to the shorter duration of sample collection (over 24 hours in children versus 48 hours in adults). Oral clearance per kilogram body weight was approximately double.

Current OTC monograph labeling for diphenhydramine HCl indicates children 12 years and above be administered the adult dose and children 6 to < 12 years of age be administered ½ the adult dose. A physician should be consulted for the dose of diphenhydramine for children < 6 years of age, although the dose of other OTC monograph ingredients in this age group is ¼ the adult dose.[12] Before health authorities provided guidelines on the development of drugs for pediatric populations, selection of doses was based empirically on body weight and/or age because pharmacokinetic and efficacy data were generally limited or unavailable. For some OTC medicines, the label advises parents and caregivers to use a child's weight to determine the right dose of medicine.[13] If the child's weight is unknown, the label instructs parents and caregivers to use age. For other OTC medicines, including antihistamines like diphenhydramine HCl, weight-based dosing is not included on the label, and parents and caregivers are instructed to use age to determine the right dose

The main purpose of this study was to characterize diphenhydramine pharmacokinetics following a single oral dose in children ages 2 to 17 years using a weight- and age-based dosing schedule with more tiers than the current age-based dosing schedule recommended by the OTC monograph. Because body size increases markedly in the two children's groups, from ages 2 to 5 years and 6 to 11 years, the additional dosing tiers were anticipated to provide more comparable systemic exposure of diphenhydramine by increasing the doses for the older children within each age range.

Methods

Study Design and Participants

The study was conducted in accordance with the tenets of the Code of Federal Regulations, and complied with the International Conference on Harmonization Good Clinical Practice guidelines. The study was reviewed and approved by Arkansas Research Medical Testing, LLC, Institutional Review Board (Little Rock, Arkansas). A parent or legal guardian provided written informed consent for a child to participate in the study, and written assent was obtained from children ≥ 6 years of age.

This open-label, single-dose, pharmacokinetic study was conducted at Arkansas Research Medical Testing, LLC. Children ages 2 to 11 years and adolescents ages 12 to 17 years, who weighed at least 24 pounds and were between the 5th and 95th percentiles for height and weight based on age and gender, were eligible. The protocol planned to complete at least 24 children and 18 adolescents with a history of allergic rhinitis and who were experiencing nasal symptoms due to hay fever or other respiratory allergies. Prospective children were screened by medical history, physical examination, clinical laboratory profile, vital signs, and history of prescription and nonprescription drugs, vitamins, and supplements taken within 28 days of screening. Females who had reached menarche had a negative urine pregnancy test at screening and before dose administration on the study day.

Children were excluded if they had a history or presence of clinically significant disease or other systemic conditions; a history of hepatitis B, hepatitis C, or human immunodeficiency virus; a history of drug, alcohol, or tobacco use; or a known sensitivity or allergy to diphenhydramine, red dye, or ELMA® cream. They were excluded if they had taken any prescription or nonprescription medication 7 days or 5 half-lives (which ever was longer) before the study start date, except for low-dose inhaled glucocorticoids, short-acting β_2 agonists, or oral contraceptives in postmenarchal female subjects.

Study Conduct

Subjects arrived at the clinical site on the day of dosing, and a parent or legal guardian remained with a child throughout the study's duration. They began a food fast after midnight on the night before dosing. Up to 2 hours before arriving at the clinic, subjects consumed a light breakfast consisting of 4 oz of water or low- or no-fat milk and either a bowl of nonsweetened cereal or 1-to-2 slices of toast with a pat of butter or serving of jelly. One hour after dosing, subjects were allowed water and noncaffeinated drinks, excluding apple, orange and grapefruit juice, and lunch was provided

Table 1. Weight-Age Dosing Schedule for Diphenhydramine HCl

Weight Range (lb)	Age (Years)	Dose (mg)
24–35	2–3	6.25
36–47	4–5	12.5
48–59	6–8	18.75
60–71	9–10	25
72–95	11	31.25
Not applicable	12–17	50

3 hours after dosing. Blood samples were collected over 24 or 48 hours, depending on the child's age. The subjects were monitored for adverse events by study personnel, and they were discharged from the site following completion of blood sampling and the physical examination.

Drug Administration

A single dose of diphenhydramine HCl liquid (12.5 mg/5 mL) was administered by oral syringe per the weight-age dosing schedule in Table 1 for children 2 to 11 years old, selecting the dose by body weight as the primary factor. For subjects 10 or 11 years old who weighed more than 95 pounds, but who met the weight and body mass index inclusion criteria, a maximum dose of 31.25 mg was administered. All adolescents 12 to 17 years old received the fixed dose of 50 mg, as this age group typically receives adult OTC doses. After swallowing the dose, subjects aged 2 to 5 years drank 2 oz of water, subjects 6 to 11 years drank 4 oz of water, and subjects 12 to 17 years drank 6 oz of water. Subjects were required to swallow the complete dose to continue in the study.

Blood Sampling

Three-milliliter blood samples were collected into tubes containing potassium ethylene diamine diacetic acid (K_2-EDTA) as the anticoagulant via an indwelling catheter. Samples were collected before and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 hours after dosing. In a subset of six adolescents 12 to 17 years old, the 0.5-hour sample was not collected, but additional blood samples were obtained at 30, 36, and 48 hours. Plasma was harvested and stored at -20° C until assayed.

Safety Monitoring

Safety was evaluated based on clinical observations, assessment of adverse events, a predose and end-of-study physical examination, and vital signs (blood pressure and pulse rate) measured before dosing, at 1.5 and 8 hours after dosing, and at the end of the study.

Sample Assay

Plasma samples were assayed for diphenhydramine using reverse-phase liquid chromatography with tandem mass spectrometry. The nominal range of quantitation used during the study was 0.50 to 200 ng/mL. For sample preparation, 50 μL of internal standard (deuterated diphenhydramine) was added to a 150-μL aliquot of human plasma. Diphenhydramine and its internal standard were recovered by liquid-liquid extraction with 1.0 mL methyl tertiary-butyl ether. The mixture was vortexed and centrifuged, and the organic layer was transferred to a 2 mL 96-well block. After evaporating the organic layer under nitrogen at −50°C, the samples were reconstituted with 100 μL of acetonitrile.

The instrument included the Shimadzu LC-AD vp pump and Shimadzu SCL-10A vp controller. The Discovery® RP Amide C16 column, 10 cm x 3mm, 5μm, with an Upchurch Scientific or equivalent 2μm PEEK frit was used. The mobile phase consisted of acetonitrile (80% solvent A) and 10 mM NH_4OAc in H_20 (20% solvent B). Operating conditions for the pump included a stop time of 1.0 min, pressure limits of 0 to 4000 psi, and total isocratic flow rate of 1000 μL/min. The column was maintained at room temperature, and injection volume was 10 μL. Transition ions m/z 256.21 → 167.01 and m/z 259.17 → 166.99 were monitored for diphenhydramine and the internal standard, respectively. Calibration standards were prepared at nine concentrations between 0.50 and 200.00 ng/mL, inclusive. Quality control samples were prepared at 1.50 (low), 20.00 (blind), 80.00 (middle), and 160.00 (high) ng/mL. Analyst® 1.4 Software (SCIEX) was used to determine peak areas of diphenhydramine and the internal standard. Subject sample concentrations were calculated from peak area ratios.

During method validation, the between-batch accuracy of diphenhydramine quality control samples ranged from −6.3% to −4.1%, while variability remained ≤ 4.53%. The within-batch accuracy ranged from −6.8% to 5.7%, while variability remained ≤ 3.75%. For quality control samples run during the study sample assays, interday accuracy ranged from 0.8% to 9.8%, while interday variability was ≤ 27.4%. Review of the quality control samples revealed that two sample tubes (80 and 160 ng/mL) were inadvertently switched in one run, and upon recalculation of the summary statistics, the interday variability was ≤ 16.1%.

Pharmacokinetic Analysis

Plasma concentration-time data for diphenhydramine were analyzed by noncompartmental methods using Phoenix™ WinNonlin v6.2.1 (Pharsight, Mountain View, California).[14,15] Plasma concentrations below the lower limit of quantitation that occurred before and after the maximum concentration were imputed as zero

Table 2. Demographic Information[a] for Pediatric Subjects by Age Group

	2 to 5 Years (n = 8)	6 to 11 Years (n = 16)	12 to 17 Years (n = 18)
Age (years)			
Mean	3.8	8.3	14.6
SD	1.04	1.69	1.85
Body weight (kg)			
Mean	17.3	29.9	55.3
SD	3.60	6.76	9.06
Minimum, maximum	11.3, 22.6	21.3, 43.1	35.4, 68.9
Body mass index (kg/m^2)			
Mean	15.3	16.6	20.8
SD	1.16	1.86	2.26
Minimum, maximum	14, 18	14, 20	16, 24
Race			
White	2	4	5
Black	4	10	13
Hispanic	2	2	0
Sex			
Female	3	9	9
Male	5	7	9

[a]Data reported as arithmetic mean and standard deviation (SD).

and missing, respectively. Actual sampling times were used in the analysis.

The maximum plasma concentration (C_{max}) and the time at which the maximum occurred (T_{max}) were determined from individual plasma concentration-time profiles. The terminal exponential rate constant (β) was estimated using linear least-squares regression of the terminal phase of the log concentration-time profile. The terminal exponential half-life (t½,β) was obtained as $0.693/\beta$. Area under the plasma concentration-time curve up to the last observed quantifiable concentration (AUC_{tlast}) was determined using the linear trapezoidal rule. Area under the plasma concentration-time profile from zero to infinite time (AUC) was the sum of AUC_{tlast} and the extrapolated area based on the ratio of the last observed quantifiable plasma concentration and terminal rate constant (Cp/β).

Oral clearance (CL/F), uncorrected for bioavailability (F), was estimated as Dose/AUC. The doses of free base diphenhydramine were used in the latter calculation, which were obtained by multiplying by 0.88. In addition, CL/F was allometrically scaled by body weight (BW) to a 70-kg adult using the approach outlined by Anderson et al: $CL/F,scaled = (CL/F)/(BW/70\ kg)^{3/4}$.[16,17]

Statistical Analysis

The relationships of observed and scaled CL/F with age were assessed using linear regression analysis. Least-squares estimates of the intercept and slope, the squared correlation coefficients, and p-values were obtained for each analysis. An age-related change was concluded if the *p-value* associated with the slope was < 0.05 for a two-sided test. This statistical analysis was conducted using SAS version 9.2.

Results

Subjects Demographics

Forty-two (42) children and adolescents with nasal symptoms due to hay fever or other respiratory allergies were enrolled in and completed the study. Their demographic information is summarized in Table 2. A minimum of two subjects per age, except for 2 years, were enrolled. There was an equal number of male and female subjects, and the majority was African American (64%). Body weight increased with age as expected, whereas body mass index (BMI) was similar in children ages 2 to 5 and 6 to 11 years and was about 35% higher in the adolescents, ages 12 to 17 years.

Diphenhydramine Pharmacokinetics

Diphenhydramine plasma concentration-time profiles following single oral doses are displayed by three age groups in Figure 1, and corresponding pharmacokinetic parameters are summarized in Table 3. These age groups represent those most commonly used in dosing schedules of OTC medicines. Both C_{max} and AUC increased with dose from the youngest to oldest age group. However, median times of the maximum concentrations (1.5 hours) and mean terminal exponential half-lives (~8 hours) were similar across age groups. In addition, half-lives of 8.4 and 9.1 hours were similar between two sets of adolescent subjects with blood sampling over 24 and 48 hours, respectively.

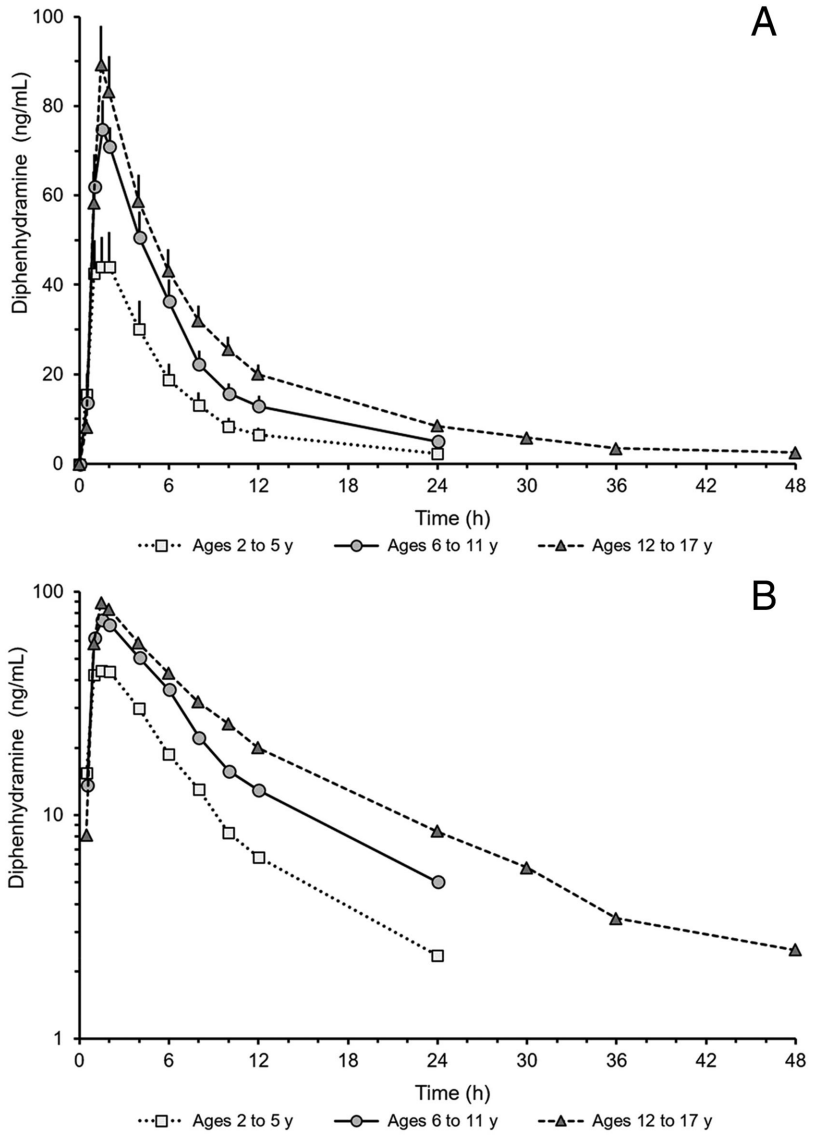

Figure 1. Mean (SE) diphenhydramine plasma concentration–time profiles by age group on regular (A) and logarithm (B) scales.

Intersubject variability for C_{max} and AUC was highest for the youngest age group and comparable for the two older age groups.

A scatter plot of individual estimates of observed and scaled oral clearance by age is shown in Figure 2. Observed oral clearance was positively and modestly correlated with age ($r^2 = 0.383$, slope p-value < 0.0001). By contrast, oral clearance did not correlate with age after allometric scaling ($r^2 = 0.015$, slope p-value $= 0.440$).

Safety Results

Forty (40) subjects reported 42 adverse events, and none was deemed serious. Forty of the adverse events were somnolence, and two were agitation. All of them were rated as mild and considered possibly or probably related to treatment by the investigator. Somnolence rates were similar across age groups with six of eight subjects ages 2 to 5 years and all subjects ≥ 6 years experiencing somnolence. Two subjects experienced a single episode of mild agitation: one 6-year-old, African-American child with a BMI of 16 kg/m^2 who received a dose of 12.5 mg (0.59 mg/kg) diphenhydramine HCl, and a second 8-year-old, African-American child with a BMI of 15 kg/m^2 who received a dose of 18.75 mg (0.72 mg/kg). No clinically relevant changes were observed in vital signs or from the end-of-study physical examination for any subject.

Discussion

In this study, diphenhydramine pharmacokinetics following a single oral dose were characterized in children

Table 3. Mean (CV%)[a] Diphenhydramine Pharmacokinetics Summarized by Age Group

Pharmacokinetic Parameter	2 to 5 Years (n = 8)	6 to 11 Years (n = 16)	12 to 17 Years (n = 18)
Dose (mg)	10.2 (45.8%)	24.2 (26.4%)	50 (0%)
Dose (mg/kg)	0.556 (28.0%)	0.807 (11.8%)	0.930 (18.7%)
C_{max} (ng/mL)	48.52 (49.2%)	83.72 (32.4%)	92.70 (40.9%)
T_{max}[b] (h)	1.5 (1.0–2.0)	1.5 (1.0–6.0)	1.5 (1.0–2.0)
AUC (ng·h/mL)	326.4 (56.9%)	587.0 (41.4%)	795.5 (45.7%)
CL/F,obs (mL/min)	510.9 (33.3%)	652.0 (29.3%)	1094 (43.1%)
CL/F, scaled (mL/min; scaled to 70 kg)	1486 (36.4%)	1260 (29.7%)	1291 (36.4%)
t½, β (h)	7.62 (22.3%)	8.47 (22.3%)	8.61 (18.9%)

[a]Arithmetic mean and percent coefficient of variation.
[b]Median (minimum–maximum).

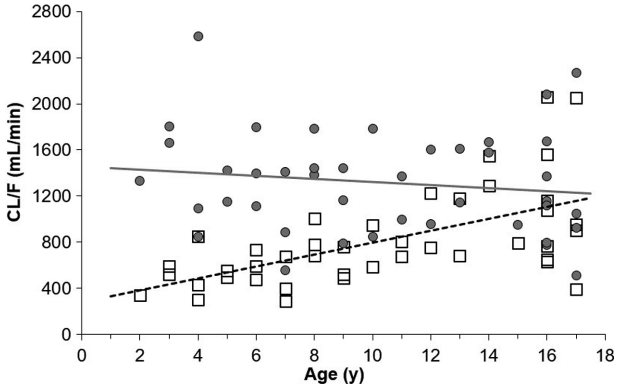

Figure 2. Relationships of diphenhydramine oral clearance (CL/F,obs γ) and allometrically scaled oral clearance (CL/F, scaled) with age (CL/F, obs = 243.3 + 56.47 × age; $P_{slope} < .0001$; $r^2 = 0.383$; CL/F, scaled = 1438 − 12.02 × age; $P_{slope} = 0.440$; $r^2 = 0.015$).

and summarized by three commonly demarcated age groups: 2 to 5 years, 6 to 11 years, and 12 to 17 years. No published pharmacokinetic data are available for the youngest age group ages 2 to 5 years. Relative to the older children and adolescents in this study, times to achieve maximum concentrations were the same, and mean t½,β was an hour shorter. Both AUC and C_{max} were lower, which corresponds to lowest doses given to children in this youngest age group.

Results for children, ages 6 to 11 years, agree with those previously reported in a group of children with a mean age of 8.9 years.[7] Mean C_{max} was 83.7 ng/mL compared with 81.8 ng/mL, and mean AUC was 587 ng·h/mL compared with 475 ng·h/mL. Time to achieve maximum concentrations is also similar, 1.5 hours compared with 1.3 hours, whereas mean t½,β appears to be somewhat longer in the current study (8.5 hours versus 5.4 hours). The shorter t½,β may be one contributing factor for the dose-dependent exposure parameters being similar despite the administered dose being about 40% higher in the previous study, leading to an underestimation of AUC. Other possible factors are differences in assay methods and the range of ages of the eight children.

Results for the adolescents, ages 12 to 17 years, who received the fixed dose of 50 mg diphenhydramine HCl agree with those reported in adults at the same dose.[5,6] Mean C_{max} was 92.7 ng/mL compared with 66.3 and 87.6 ng/mL, and mean AUC was 796 ng·h/mL compared with 667 and 775 ng·h/mL. Time to achieve maximum concentrations is shorter, 1.5 hours compared with 2.3 and 2.2 hours, whereas mean t½,β of 8.6 hours is comparable with 9.2 and 9.8 hours. The shorter T_{max} may reflect the difference in dosage forms among studies, as the current study dosed a liquid formulation compared with solid caplets[5] and tablets[6] in the adult studies. This difference persisted even though the adolescents were permitted to consume a light breakfast (not within 2 hours before dosing), compared with continued fasting for 4 hours post-dose by the adults.[5,6]

Ideally a pediatric dosing schedule should provide systemic drug exposure (C_{max} and AUC) that is comparable among children despite large differences in body size associated with age. In this study, C_{max} and AUC increased over the age range of 2 to 17 years with increasing doses, which was anticipated because the weight-age dosing schedule was based on Clark's rule rather than on oral clearance. This rule assumes a linear relationship of body weight and dose.[18] Nevertheless, the dosing schedule included diphenhydramine HCl doses over an eightfold range (6.25 mg to 50 mg), and yet, achieved mean C_{max} and AUC that differed only about twofold across age groups. The times to maximum concentrations and terminal exponential half-lives were similar.

Observed oral clearance for diphenhydramine increased markedly with age as expected due to increasing body size. Application of allometric scaling often separates the co-varying effects of growth (weight) and maturation (age) on this pharmacokinetic parameter.[16] Following allometric adjustment, no age-related change

in oral clearance was apparent, indicating no maturation effect on diphenhydramine clearance in children 2 years of age or greater. A similar result in children was observed for another OTC antihistamine, doxylamine,[19] where oral clearance after allometric scaling was unrelated to age.

No serious adverse events were reported in this study. Almost all subjects reported experiencing somnolence, which was considered mild by the investigator and possibly or probably related to drug. Somnolence is consistent with the side effect profile for diphenhydramine in children and adults.[20]

Conclusion

The pediatric weight-age dosing schedule for diphenhydramine HCl evaluated in this study extended over an eightfold range, providing C_{max} and AUC that increased only about twofold across age groups. Oral clearance increased with age, but after allometric scaling, no age-related difference was observed. The safety profile observed in this study was consistent with the known profile for diphenhydramine, with mild somnolence being experienced by almost all subjects.

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Declaration of Conflicting Interests

This study was supported by Johnson & Johnson Consumer, Inc., McNeil Consumer Healthcare Division. C Gelotte and B Zimmerman were employees at the time the study was conducted and the manuscript prepared, and have or owned Johnson & Johnson stock. The sponsor designed the study, provided funding for the research, conducted the analysis, wrote the final clinical study report, and edited this manuscript. G Thompson, who drafted the manuscript, is a paid consultant to the Consumer Healthcare Products Association of which McNeil Consumer Healthcare is a member.

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