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Brompheniramine and Chlorpheniramine Pharmacokinetics Following Single-Dose Oral Administration in Children Aged 2 to 17 Years

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Abstract

Two pediatric studies characterized brompheniramine and chlorpheniramine pharmacokinetics in a total of 72 subjects, aged 2 to 17 years. A single age-/weight-based oral dose, ranging from 1 to 4 mg, was administered with 2 to 6 oz of water at least 2 hours after a light breakfast. Plasma samples were obtained before and for 72 hours after dosing and analyzed using high-pressure liquid chromatography–tandem mass spectrometry. Pharmacokinetic parameters were estimated using noncompartmental methods; relationships with age were assessed using linear regression. Results indicated that for brompheniramine and chlorpheniramine, C_{max} was similar across age groups, although it tended to occur earlier in the youngest group. AUC was ~15% to 30% higher in the oldest age group. As expected, CL_o and V_z/F increased with age; however, following allometric scaling, no age-related differences existed. Because the increase with age for both parameters was similar, no age-related differences in $t_{1/2,z}$ existed (~15 hours). Overall, the single doses were well tolerated. Sedation was the most common reported AE and appeared to be more prevalent in the 2- to 5-year-old group. Overall, these results indicate that an age/weight dosing nomogram using a 4-fold range of doses achieves similar C_{max} and AUC.

Keywords

brompheniramine, chlorpheniramine, pediatrics, pharmacokinetics

Brompheniramine and chlorpheniramine are structurally similar, first-generation antihistamines of the alkylamine class. They are both inhibitors of H1-receptors with similar potency in in vitro receptor-binding studies[1,2] and in in vivo studies of occupancy.[3] Brompheniramine and chlorpheniramine are generally recognized as safe according to the over-the-counter (OTC) monograph (21 CFR 341.12) for the treatment of symptoms of allergic rhinitis and the common cold.

Brompheniramine pharmacokinetics have been characterized in children and adults following single-dose oral administration of 4 and 9.8 mg, respectively.[4,5] Results from these studies indicated that peak concentrations occurred at ~3 hours, with peak concentrations ~50% higher in adults (11.6 versus 7.7 ng/mL). Oral clearance was ~3-fold higher in children (20.2 versus 6.0 mL/min/kg), the terminal volume of distribution was ~2-fold larger in children (20 versus 11.7 L/kg), and the terminal exponential half-life was decreased ~50% in children (12.4 versus 24.9 hours). Brompheniramine is primarily metabolized to monodesmethyl and didesmethyl metabolites, with approximately 17% of the dose recovered unchanged in urine.[6,7] The metabolic pathway(s) and pharmacological activity of the metabolites are unknown.

Chlorpheniramine pharmacokinetics have been studied in adults following single-dose intravenous and oral administration.[8] Following intravenous administration, chlorpheniramine pharmacokinetic parameters included steady-state and terminal volumes of distribution of 3.17 and 3.36 L/kg, total clearance of ~10 L/h, and a terminal exponential half-life of ~22 hours. Chlorpheniramine pharmacokinetics have also been assessed following single-dose oral administration of an 8-mg tablet and a 10-mg solution.[8] Results from both formulations were very similar, with a peak concentration of 17.9 ng/mL occurring 2.8 hours following oral administration. Absolute

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bioavailabilities following oral administration of a solution and tablet formulation were ~47% and 35%, respectively, with ~20% of the dose recovered in urine. Comparison of results in children[9] with those obtained in adults indicated that in children, clearance was increased ~50%, with a corresponding decrease in the terminal exponential half-life of ~50%, with no change in the terminal volume of distribution. Chlorpheniramine metabolism has been assessed following oral and intravenous administration.[10,11] Results indicated that chlorpheniramine was extensively metabolized with 2 metabolites, didesmethyl and monodesmethyl chlorpheniramine, occurring via n-dealkylation, with ~20% excreted unchanged in urine. More recent studies have indicated that chlorpheniramine metabolism is mediated in part via cytochrome P450 (CYP) 2D6[12] and does not appear to involve CYP2C9[13]; the metabolites associated with the CYP2D6 pathway have not been identified. The pharmacological activity of the metabolites is unknown.

Historically, dosing in pediatric patients has been empirically based on body weight (BW) and/or age because 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 older should be administered the adult dose, and children 6 to <12 years of age be administered one-half the adult dose. For children <6 years of age, a physician should be consulted.[14]

The primary purpose of these 2 clinical studies was to characterize the pharmacokinetic profiles of brompheniramine and chlorpheniramine following single-dose oral administration in children over the range of 2 to 17 years of age using an age/weight nomogram.

Methods

Study Design

Both studies were reviewed and approved by Compass Institutional Review Board, Mesa, Arizona. Written informed consent (parent/guardian)/assent (children 6 to 17 years of age) was obtained prior to any study-related procedures.

Both studies were conducted as a single-dose, open-label, single-center study. For each drug, approximately 30 children were to be enrolled with the goal of completing 24 children, with a minimum of 12 subjects 2 to 6 years of age. The study population consisted of nonsmoking, healthy children aged 2 to 17 years. Subjects had a minimum weight of 10.9 kg and a body weight within the 5th and 95th percentile based on their height, weight, body mass index, age, and sex. Subjects had a history of allergic rhinitis (symptomatic or asymptomatic), symptoms of an acute upper respiratory infection, or risk of developing an upper respiratory infection based on empiric criteria. A child was considered asymptomatic but at risk based on frequency of infections, size of the family, and exposure to a family member who was ill, or a child who was attending school. Exclusion criteria included a known sensitivity to antihistamines, systolic and/or diastolic blood pressure above the 95th percentile based on age, height, and sex, any use of drugs except low-dose inhaled glucocorticoids or short-acting beta-2 agonist for 72 hours and no H-1 receptor antagonist for 7 days prior to dosing, a history of drug or alcohol abuse, or use of an investigational product within 30 days.

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 (eg, toast or nonsweetened cereal with 4 oz of water or low-/no-fat milk) at least 2 hours prior to dosing. Subjects were allowed clear noncaffeinated liquids or fruit juice (other than grapefruit, apple, or orange) beginning 1 hour after dosing but otherwise continued to fast until 3 hours after dosing. Subjects could leave the clinical site following the 24-hour blood sample, returning for 48- and 72-hour assessments.

Drug Administration

A single dose of brompheniramine maleate (0.2 mg/mL) or chlorpheniramine maleate (0.2 mg/mL) solution based on age and/or weight was administered by oral syringe, as listed in Table 1. The solution was not a commercial product and was manufactured solely for this study. For children 2 to 11 years of age, the dose was 1 to 3 mg and was based on body weight. For children 12 to 17 years of age, the dose was 4 mg and was independent of body weight.

For subjects aged 2 to 5 years, 2 oz of water and for subjects aged 6 to 17 years, 6 oz of water was consumed with the dose. Subjects were required to swallow the complete dose to continue in the study.

Blood Sampling

For brompheniramine and chlorpheniramine, 3.0 mL of blood was collected prior to and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after dosing. Blood samples were obtained via an indwelling catheter or venipuncture. Plasma containing sodium heparin was harvested and stored at -20°C or less until assayed.

Safety Monitoring

Safety was evaluated based on clinical observations and assessment of adverse events (AEs), vital signs (blood pressure and heart rate prior to dosing and every hour

Table 1. Administered Dose Based on Age and Weight and the Number of Subjects Administered Each Dose

Age (Years)	Weight Range (kg)	Dose (mg)	Brompheniramine (n)	Chlorpheniramine (n)
2–3	10.9 to <16.4	1.0	4	6
4–5	16.4 to <21.8	1.5	9	5
6–8	21.8 to <27.3	2.0	4	2
9–10	27.3 to <32.7	2.5	2	5
11	32.7 to <43.2	3	5	5
12–17	Not applicable	4	13	13

after dosing for 6 hours and at the end of the study), and predose and end-of-study physical examinations. Additional sedation assessments were also evaluated as described in the Sedation Monitoring section below and were also included as part of assessment of AEs obtained during the study.

Sedation Monitoring

Assessments of sedation using the University of Michigan Sedation Scale (UMSS) as developed by Malviya[15,16] were completed at baseline, every hour for 6 hours following dosing, and subsequently at the discretion of the investigator. The UMSS is a validated 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 (subject can only be aroused with significant physical stimulation);
4 = Unarousable.

Bioanalytical Assay

For brompheniramine, 100 μL of plasma and 25 μL of the internal standard working solution (20 ng/mL brompheniramine-d_6 maleate) underwent protein separation using 300 μL acetonitrile. The supernatant (100 μL) was diluted with 400 μL 0.1% formic acid and analyzed via high-pressure liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) using positive ion electrospray. The nominal range of quantitation used during the study was 0.050 to 20 ng/mL based on a 0.1-mL aliquot of human plasma. Based on brompheniramine quality control (QC) samples run during validation (0.05 to 15 ng/mL), interday variability was 4.44% or less, and interday accuracy ranged from 0.939% to 2.75%; intraday variability was 11.1% or less, and the intraday accuracy ranged from -6.1% to 1.79%. For QC samples run during the study sample assays (0.125 to 15 ng/mL), interday variability was 6.64% or less, and interday accuracy ranged from -5.33% to 0.156%. All samples were analyzed within the established stability time (54 days).

For chlorpheniramine, 50 μL of plasma with 25 μL of the internal standard working solution (25 ng/mL brompheniramine) underwent protein separation using 350 μL of acetonitrile. Fifty microliters of the supernatant was diluted with 400 μL of 0.1% formic acid and analyzed via HPLC-MS/MS using positive ion electrospray. The nominal range of quantitation used during the study was 0.25 to 50 ng/mL. Based on chlorpheniramine QC samples run during validation (0.25 to 40 ng/mL), interday variability was 11.6% or less, and interday accuracy ranged from -1.1% to 3.73%; intraday variability was 6.05% or less, and the intraday accuracy ranged from -1.98% to 9.27%. For QC samples run during the study sample assays, interday variability was 7.24% or less, and interday accuracy ranged from -1.83% to 1.52%. All samples were analyzed within the established stability time (250 days).

Pharmacokinetic Analysis

Individual brompheniramine or chlorpheniramine plasma concentration–time profiles were analyzed using noncompartmental analyses.[17,18] The maximum plasma concentration (C_{max}) and the time at which the maximum occurred (T_{max}) were determined from the individual plasma concentration–time profiles. The terminal exponential rate constant (λ_z) was determined using linear least-squares regression of the terminal phase of the log concentration–time profile (minimum of 3 data points required). The terminal exponential half-life ($t_{1/2,z}$) was obtained as $0.693/\lambda_z$. Area under the plasma concentration–time curve (AUC_{tlast}) was determined up to the last observed quantifiable concentration, using the linear trapezoidal rule. The extrapolated area under the plasma concentration–time curve (AUC_{ext}) 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_{tlast} and AUC_{ext}. Using the amount of the base administered (dose [D]), oral clearance (CL_o), and terminal volume of distribution

(uncorrected for bioavailability; V_z/F) were determined as D/AUC and CL_o/λ_z, respectively. In addition, CL_o and V_z/F were allometrically scaled based on the approach outlined by Anderson and Holford (ie, CL_o allometric = $CL_o/[BW/70\ kg]^{3/4}$; V_z/F allometric = $V_z/F/[BW/70\ kg]$),[19] and CL_o was also isometrically scaled ($CL_o/BW = CL_o/BW$). Pharmacokinetic parameters were estimated using WinNonlin v5.1.

Statistical Analysis

The relationships between CL_o, CL_o allometric, CL_o/BW, V_z/F, and V_z/F allometric and age were 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. Statistical significance of an age-related change was concluded if the *P* value associated with the slope was < 0.05 for a 2-sided test. All statistical analyses were conducted using SAS version 9 or later.

Results

Subjects Demographics

For brompheniramine, 37 subjects were enrolled in the study, with 36 subjects completing the study. One subject (12-year-old male) was discontinued from the study because of uncooperativeness. For chlorpheniramine, 36 subjects were enrolled, and all subjects completed the study. The number of subjects administered each dose is summarized in Table 1. Demographics for subjects enrolled in the study are summarized in Table 2. For each age group, there was a minimum of 2 subjects. For brompheniramine and chlorpheniramine, subjects were similar for sex, whereas the majority of subjects were African American (78% and 75%, respectively) and of non-Hispanic or Latino ethnicity (86% and 89%, respectively). As expected, body weight increased with age.

Brompheniramine Exposure/Pharmacokinetics

Brompheniramine plasma concentration–time profiles following single-dose oral administration are illustrated in Figure 1A, with corresponding pharmacokinetic parameters summarized in Table 3 by age group as per the current monograph (2 to 5, 6 to 11, and 12 to 17 years old).

General, geometric mean C_{max} was similar across the age groups, although median T_{max} tended to occur earlier in the 2- to 5-year-old age group. The mean (range) percent AUC obtained via extrapolation was 5.3% (range, 1.0%–29.1%). Geometric mean AUC tended to be slightly higher (~15%) in the 12- to 17-year-old age group. The geometric mean terminal exponential half-life appeared similar across age groups. When results were subdivided by sex, AUC appeared to be lower (~25%) and $t_{1/2,z}$ appeared to be shorter (~25%) in males, whereas C_{max} and T_{max} appeared similar.

The relationships between oral clearance (allometrically scaled and isometrically scaled) and the terminal volume of distribution (allometrically scaled;

Table 2. Demographics for Pediatric Subjects Administered a Single Oral Dose of Brompheniramine or Chlorpheniramine

Brompheniramine

	Age Group		
Demographic	2 to 5 Years (n = 12)	6 to 11 Years (n = 12)	12 to 17 Years (n = 13)
Age (years)			
Mean	3.5	8.5	14.3
SD	1.0	1.8	1.8
Body weight (kg)			
Mean	16.6	29.9	52.3
SD	2.3	7.5	10.1
Height (cm)			
Mean	102.2	132.8	160.5
SD	7.3	11.3	8.8
Race			
African American	10	8	11
White	2	3	0
Asian	0	1	0
Multiracial	0	0	2
Ethnicity			
Hispanic or Latino	2	3	0
Not Hispanic or Latino	10	9	13
Sex			
Female	5	6	6
Male	7	6	7

Chlorpheniramine

	Age Group		
Demographics	2 to 5 Years (n = 9)	6 to 11 Years (n = 14)	12 to 17 Years (n = 13)
Age (years)			
Mean	3.6	8.5	14.5
SD	1.1	1.9	1.7
Body weight (kg)			
Mean	16.6	31.0	54.7
SD	3.4	9.4	7.6
Height (cm)			
Mean	101.8	132.8	163.5
SD	9.7	11.0	6.3
Race			
African American	7	9	11
White	1	3	0
Asian	0	1	0
Multiracial	1	1	2
Ethnicity			
Hispanic or Latino	1	3	0
Not Hispanic or Latino	8	11	13
Sex			
Female	4	7	6
Male	5	7	7

SD, standard deviation.

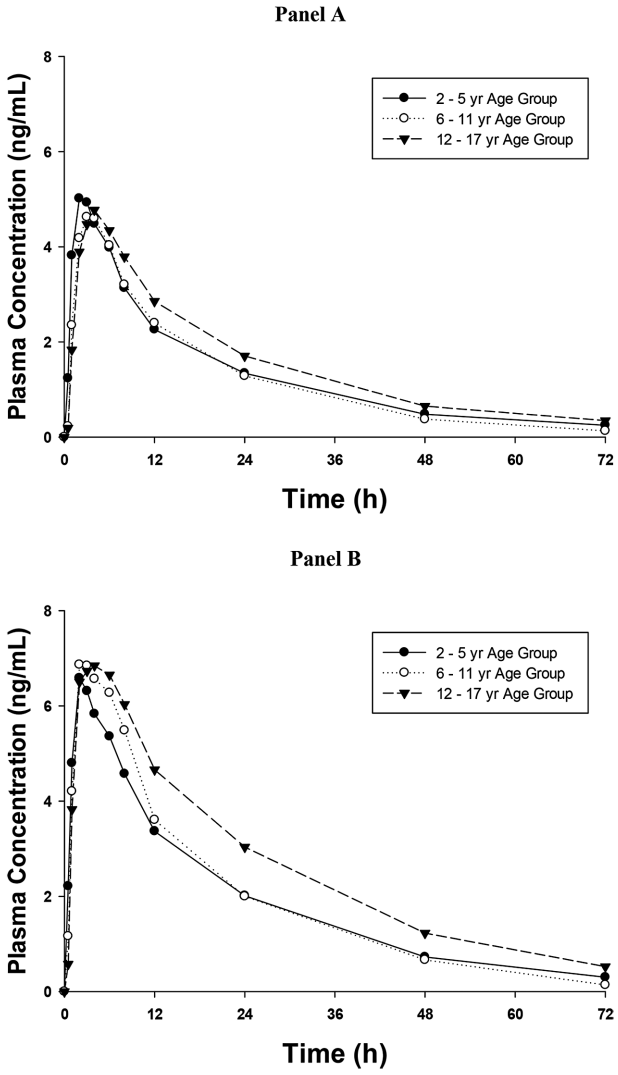

Figure 1. Mean brompheniramine (A) and chlorpheniramine (B) plasma concentration–time profiles summarized by age group following single-dose oral administration.

equivalent to isometric scaling) with age are shown in Figure 2A,B and Figure 3A, respectively. As expected, observed oral clearance was positively correlated with age (slope $P < 0.001$; figure not shown). Over the range of 2 to 17 years, the predicted oral clearance increased ~235% (10.4 to 34.9 L/h). However, allometrically adjusted oral clearance normalized to 70 kg was not statistically significantly related to age (ie, slope $P = 0.73$; Figure 2A). In addition, when oral clearance was isometrically adjusted for body weight, no statistically significant relationship with age was observed (ie, slope $P = 0.24$; Figure 2B). The observed terminal volume of distribution, unadjusted for bioavailability, also increased with age (slope $P < 0.001$; figure not shown), whereas the allometrically adjusted terminal volume of distribution appeared to be unrelated to age (slope $P = 0.083$; Figure 3A). Over the range of 2 to 17 years, the predicted terminal volume of distribution increased ~290% (183 to 714 L, respectively), whereas the allometrically scaled volume of distribution, adjusted to 70 kg, was independent of age (ie, predicted V_z/F via intercept, 1030 L, corresponding to 14.7 L/kg). Based on allomeric theory, the terminal exponential half-life should increase based on $BW^{0.2519}$. However, in this study, the observed terminal exponential half-life was not related to body weight or age (predicted $t_{1/2,z}$ via intercept, 14.5 hours; figure not shown). This may be in part because of the relatively small change expected over the range of body weight within this study (~35% increase) and the variability across subjects.

Chlorpheniramine Exposure/Pharmacokinetics

Chlorpheniramine plasma concentration–time profiles following single-dose oral administration are illustrated in Figure 1B with corresponding pharmacokinetic parameters summarized in Table 3 by age group (2 to 5, 6 to 11, and 12 to 17 years).

Geometric mean C_{max} was similar across the age groups, although median T_{max} tended to occur earlier in the 2- to 5-year-old age group. The mean (range) percent AUC obtained via extrapolation was 9.4% (range, 2.9%–19.5%). Geometric mean AUC tended to be slightly higher (~30%) in the 12- to 17-year-old age group. The geometric mean terminal exponential half-life appeared similar across age groups. When results were subdivided by sex, AUC appeared to be lower in males (~25%), whereas C_{max}, T_{max}, and $t_{1/2,z}$ appeared similar.

The relationship between oral clearance (allometrically scaled and isometrically scaled) and the terminal volume of distribution (allometrically scaled; equivalent to isometric scaling) with age are shown in Figures 2C,D and 3B, respectively. As expected, observed oral clearance was positively correlated with age (slope $P < 0.001$; figure not shown). Over the range of 2 to 17 years, the predicted oral clearance increased ~305% (5.41 to 22.0 L/h). However, when oral clearance was allometrically scaled, no significant relationship with age existed (ie, slope $P = 0.57$; Figure 2C). In addition, when oral clearance was isometrically adjusted for body weight, no statistically significantly relationship with age was observed (ie, slope $P = 0.34$; Figure 2D). As expected, the observed terminal volume of distribution, unadjusted for bioavailability, also increased with age (slope $P < 0.001$; figure not shown), whereas the allometrically adjusted terminal volume of distribution did not appear to be related to age (slope $P = 0.067$; Figure 3B). Over the range of 2 to 17 years, the predicted observed terminal volume of distribution increased ~305% (112 to 453 L), whereas the allometrically scaled volume of distribution, adjusted to

Table 3. Geometric Mean (CV%) for Brompheniramine and Chlorpheniramine Pharmacokinetics Summarized by Age and Sex Following Single-Dose Oral Administration

Brompheniramine					
PK Parameter	Age Group 2–5 Years (n = 12)	Age Group 6–11 Years (n = 12)	Age Group 12–17 Years (n = 12)	Males (n = 19)	Females (n = 17)
Cmax	5.3	4.8	4.9	4.8	5.3
(ng/mL)	(23.1%)	(21.8%)	(31.2%)	(29.5%)	(19.4%)
Tmax[a]	3.00	4.00	3.00	3.00	3.00
(h)	(1.00–4.00)	(2.00–6.00)	(2.00–8.00)	(1.00–8.00)	(1.00–4.02)
AUC	91.85	87.55	107.1	82.25	112.0
(ng·h/mL)	(51.1%)	(31.7%)	(60.7%)	(45.2%)	(46.5%)
CLo	10.48	20.11	27.37	20.15	15.74
(L/h)	(65.1%)	(35.4%)	(60.8%)	(70.9%)	(71.1%)
CL_o allometric	30.99	38.84	33.64	39.70	29.20
(L/h; normalized to 70 kg)	(58.39%)	(33.59%)	(60.59%)	(48.06%)	(50.01%)
CL_o/BW	635.5	691.1	514.8	710.9	512.6
(mL/h/kg)	(56.7%)	(35.3%)	(61.2%)	(48.6%)	(50.6%)
Vz/F	222.8	389.1	623.6	374.3	382.4
(L)	(36.6%)	(24.6%)	(23.9%)	(59.3%)	(50.1%)
Vz/F allometric	945.8	936.2	820.9	924.6	871.5
(L; normalized to 70 kg)	(25.7%)	(15.4%)	(24.0%)	(24.0%)	(20.9%)
V_z/BW	13.51	13.37	11.73	13.21	12.45
(L/kg)	(25.7%)	(15.4%)	(24.0%)	(24.0%)	(20.9%)
t1/2,z	14.7	13.4	15.8	12.8	16.8
(h)	(40.1%)	(21.9%)	(41.5%)	(30.8%)	(34.5%)
Chlorpheniramine					
PK Parameter	Age Group 2–5 Years (n = 9)	Age Group 6–11 Years (n = 14)	Age Group 12–17 Years (n = 13)	Males (n = 19)	Females (n = 17)
Cmax	6.8	7.3	7.3	6.8	7.6
(ng/mL)	(29.5%)	(26.6%)	(40.4%)	(35.7%)	(27.1%)
Tmax[a]	2.00	3.00	3.00	3.00	3.00
(h)	(2.00–4.00)	(2.00–6.00)	(2.00–8.00)	(2.00–8.00)	(2.00–6.00)
AUC	133.5	136.7	174.6	139.2	159.5
(ng·h/mL)	(49.2%)	(35.4%)	(66.9%)	(52.7%)	(50.7%)
CLo	6.23	12.10	16.10	12.01	10.69
(L/h)	(61.6%)	(33.4%)	(66.9%)	(77.6%)	(58.1%)
CL_o allometric	18.56	22.97	19.50	21.58	19.41
(L/h; normalized to 70 kg)	(54.2%)	(28.6%)	(64.2%)	(51.5%)	(47.0%)
CL_o/BW	381.7	406.2	296.8	374.8	338.3
(mL/h/kg)	(52.8%)	(30.6%)	(63.8%)	(50.8%)	(51.2%)
Vz/F	138.7	251.2	373.9	261.6	237.5
(L)	(31.8%)	(35.4%)	(33.4%)	(60.7%)	(46.0%)
Vz/F allometric	595.0	590.0	482.4	571.7	526.3
(L; normalized to 70 kg)	(25.3%)	(19.5%)	(30.8%)	(29.1%)	(24.0%)
V_z/BW	8.50	8.43	6.89	8.17	7.52
(L/kg)	(25.3%)	(19.5%)	(30.8%)	(29.1%)	(24.0%)
t1/2,z	15.4	14.4	16.1	15.1	15.4
(h)	(37.2%)	(20.0%)	(41.1%)	(32.3%)	(33.7%)

C_{max}, maximum plasma concentration; T_{max}, time corresponding to the maximum plasma concentration; AUC, area under the plasma concentration–time profile from time zero to infinity; CL_o, oral clearance; CL_o, allometric scaled oral clearance, normalized to 70 kg; CL_o/BW, body weight isometrically scaled oral clearance; V_z/F, terminal volume of distribution, unadjusted for bioavailability; V_z/F, allometric scaled terminal volume of distribution, uncorrected for bioavailability and normalized to 70 kg; Vz/BW, body weight isometrically scaled terminal volume of distribution, uncorrected for bioavailability; $t_{1/2,z}$, terminal exponential half-life.
[a]Median (range).

70 kg, was independent of age (ie, predicted V_z/F via intercept, 657 L, corresponding to 9.38 L/kg). Similar to brompheniramine, no increase was observed for the terminal exponential half-life with body weight or age (predicted $t_{1/2,z}$ via intercept, 15.4 hours; figure not shown); this may also be related to the small increase expected (~35%) and the variability across subjects.

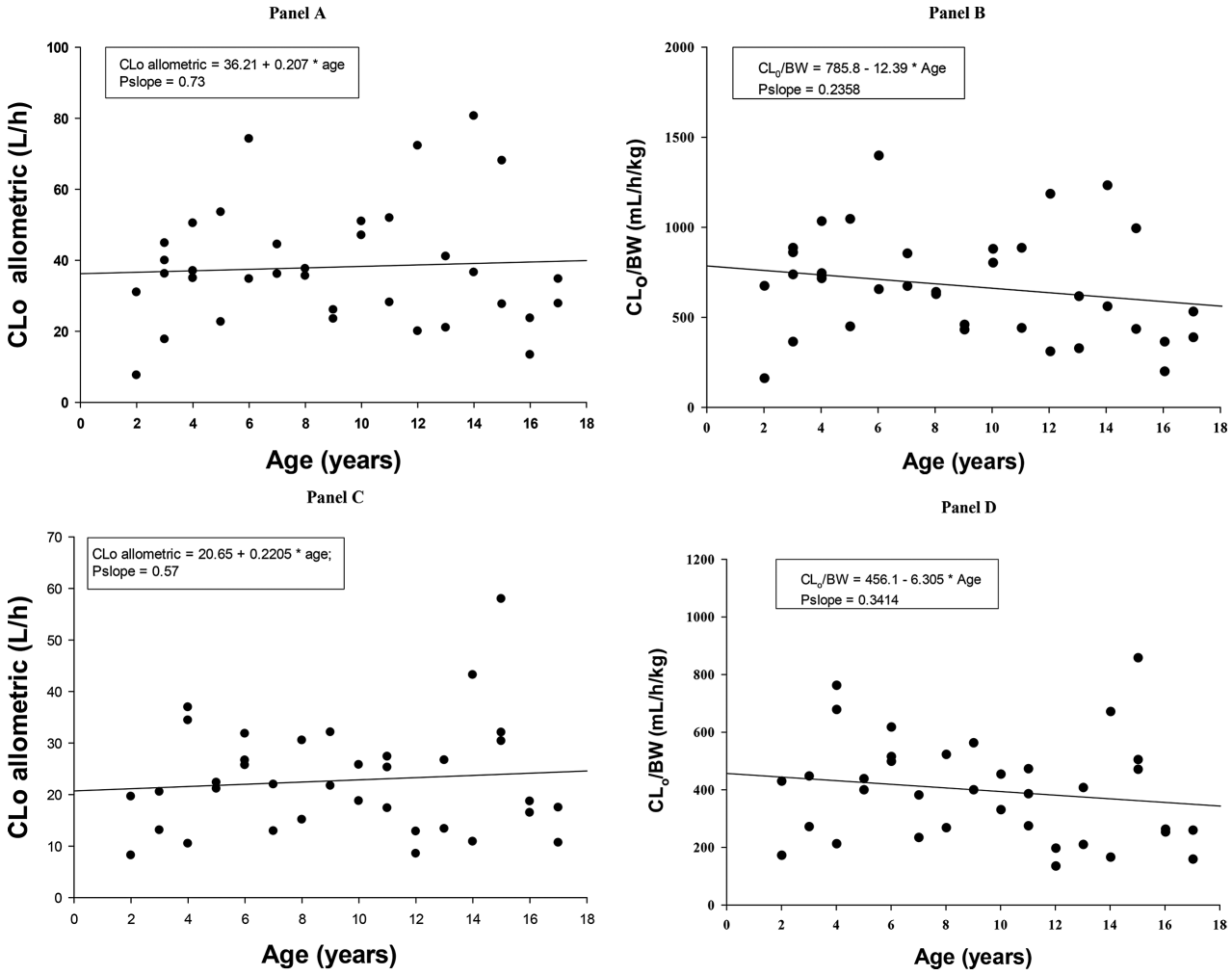

Figure 2. Relationship between brompheniramine and chlorpheniramine allometrically scaled oral clearance (CL_o, allometric; A and C, respectively) and body weight isometrically scaled oral clearance (CL_o/BW; B and D, respectively) and age following single-dose oral administration.

Safety Results. For brompheniramine and chlorpheniramine, no serious adverse events (AEs) or withdrawals because of AEs were reported in the study.

Brompheniramine. Seven subjects (18.9%) reported 7 AEs during the study. Four of the AEs were mild, and 3 were moderate. AEs included 5 events of sedation, 1 event of malaise, and 1 event of pain at the site of blood sampling. Sedation was rated as drug related, whereas the other AEs were considered not drug related. The incidence of sedation was more frequent in the youngest age group (33.3% versus 8.3% and 0%); no apparent sex difference existed (males, 15.0%; females, 11.8%). In addition, no clinically significant changes were observed in vital signs.

The majority of subjects were alert and awake during the 6-hour assessment period, and no subject was rated as deeply sedated or unarousable. Forty-nine percent of the subjects never reported any level of sedation. Thirty-two percent of the subjects experienced mild sedation at only 1 point over the 6-hour observation period. Peak sedation generally occurred at between 2 and 3 hours, with 1 subject moderately sedated at 2 hours and 2 subjects moderately sedated at 3 hours; thereafter, sedation levels decreased and remained low. Overall, 5 subjects were rated as moderately sedated; 4 subjects at 1 time point, and 1 subject at 2 time points (1 and 5 hours).

Chlorpheniramine. Eight subjects (22.2%) reported 8 AEs during the study. AEs included 7 events of sedation (6 moderate and 1 severe) and 1 event of mild headache. All were considered drug related. The incidence of sedation was more frequent in the youngest age group (33.3% versus 14.3% and 15.4%) and in males (males, 26.3%; females, 11.8%). In addition, no clinically significant changes were observed in vital signs.

The majority of subjects were alert and awake during the 6-hour assessment period, and no subject was rated unarousable. Forty-four percent of the subjects (16 of

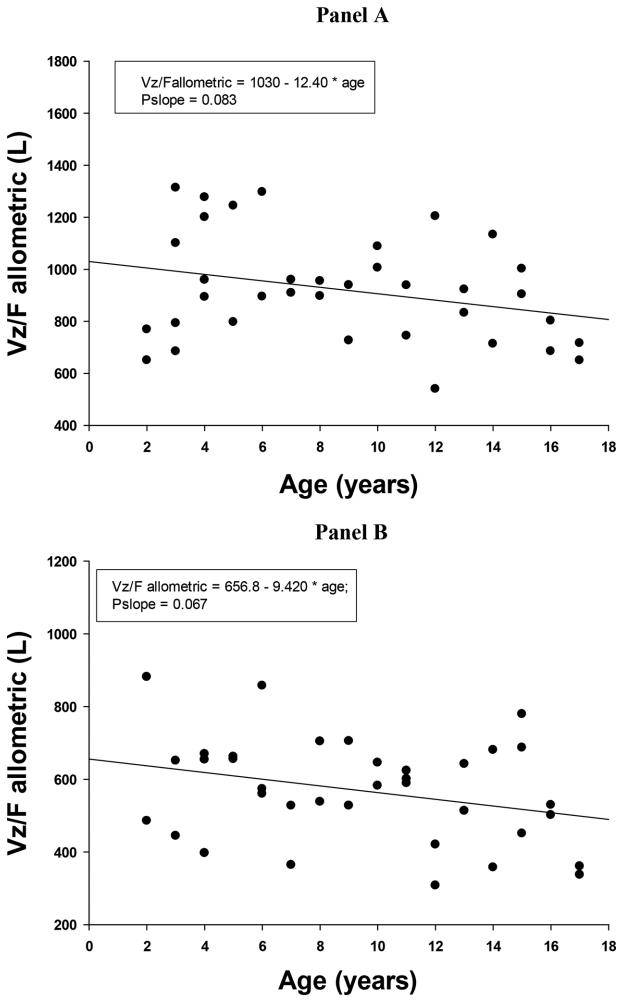

Figure 3. Relationship between brompheniramine and chlorpheniramine allometrically scaled terminal volume of distribution (V_z/F allometric; A and B, respectively) and age following single-dose oral administration.

36) never reported sedation at any time, and 22.2% of the subjects (8 of 36) reported only minimal sedation at 1 time point during the assessment period. Peak sedation generally occurred at between 2 and 3 hours, with 4 subjects rated moderately or deeply sedated; thereafter, sedation levels decreased, and by 5 hours no subject was rated moderately sedated. Of the 2 subjects rated deeply sedated, one was a 4-year-old boy rated moderately sedated at baseline, awake and alert at 1 hour, moderately sedated at 2 hours, deeply sedated at 3 hours, and awake and alert from 4 to 6 hours. The other subject was a 3-year-old boy who was deeply sedated at 1 and 2 hours and awake/alert at all other times.

Discussion

In these studies, brompheniramine and chlorpheniramine pharmacokinetics were characterized in children 2 to 17 years of age following a single oral dose of either a brompheniramine maleate or chlorpheniramine maleate solution (1 to 4 mg).

Following single-dose oral administration of brompheniramine or chlorpheniramine based on an age/weight nomogram (please see Table 1), C_{max} was generally similar across ages, although it tended to occur earlier in the 2- to 5-year-old group for chlorpheniramine (2.0 versus ~3.0 hours); please see Table 3. Systemic exposure as assessed by AUC for both drugs also appeared to be ~15% to 30% higher in the 12- to 17-year-old age group. The terminal exponential half-life for both drugs appeared to be independent of age and very similar for both drugs (~15 hours). When results were subdivided by sex, results were also very similar for both drugs, although AUC tended to be lower in males (~25%), and C_{max} and T_{max} appeared similar across sexes. However, $t_{1/2,z}$ appeared to be lower (~25%) in males for brompheniramine, whereas this trend was not observed for chlorpheniramine (please see Table 3).

As expected because of increasing body size, oral clearance for both drugs increased significantly with age (brompheniramine, slope $P < 0.001$, ~235% increase over the age range; chlorpheniramine, $P < 0.001$, ~305% increase over the age range). However, using an allometrically scaled approach as recommended by Anderson and Holford,[19] no significant relationship existed with age. Similar to oral clearance, the terminal volume of distribution also increased with increasing age. For brompheniramine, the terminal volume of distribution increased ~290% (slope $P < 0.001$), whereas chlorpheniramine terminal volume of distribution increased ~305% (slope $P < 0.001$). Similar to oral clearance, allometrically adjusted terminal volume of distribution was no longer related to age for either brompheniramine or chlorpheniramine. As a result of similar increases in oral clearance and the terminal volume of distribution, no change in the terminal exponential half-life with age was observed for either drug. 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 for brompheniramine were compared with those previously reported for children 6 to 12 years of age (n = 14),[5] good agreement was generally observed. Based on the 6- to 11-year-old age group in this study, there was good agreement between studies in the time to achieve peak concentration (4.0 hours in the current study versus 3.2 hours in the previous study). In addition, dose-adjusted systemic exposure parameters (C_{max} and AUC) were also in good agreement between studies (observed C_{max} in the current study, 4.8 ng/mL following 2 to 3 mg versus 7.7 ng/mL following 4 mg; observed AUC, 87.6 versus 127 ng·h/mL). Although

the terminal exponential half-life was similar between studies (current study, 13.4 versus 12.4 hours), brompheniramine primary pharmacokinetic parameters appeared to be slightly lower in the current study (current study, CL_o = 20.1 L/h; V_z/F = 389 L versus the literature[5]: CL_o = 38.6 L/h, V_z/F = 638 L). Although these results may represent between-study variability, based on the dose, AUC, and $t_{1/2,z}$ reported in the previous study, these differences may possibly be related to the use of the dose of the salt instead of the dose of the base for estimation of CL_o and V_z/F in the previous study. Using the dose of the base, CL_o (23 L/h) and V_z/F (411 L) appeared to be very similar to that observed in the current study.

Chlorpheniramine pharmacokinetics have also been assessed in children aged 6 to 16 years of age in a single-dose study (n = 11).[9] When results in subjects 6 to 10 years of age in the previous study were compared with children 6 to 11 years of age in the current study, results between studies were generally in good agreement. Dose-adjusted peak concentrations were slightly higher in the previous study (observed current study, 7.3 ng/mL following 2 to 3 mg versus observed in the previous study of 14.9 ng/mL following 0.12 mg/kg), consistent with a slightly earlier time to achieve peak concentrations (current study, 3.0 hours versus previous study of 2 hours). Dose-adjusted AUCs were also in good agreement (observed values in current study, 137 versus 249 ng·h/mL). Chlorpheniramine primary pharmacokinetic parameters were also similar between studies (current study, CL_o = 12.1 L/h and Vz/F = 251 L versus previous study, CL_o = 15.5 L/h and V_z/F of 224 L) as well as the terminal exponential half-life (current study, 14.4 versus 11.7 hours).

Brompheniramine and chlorpheniramine were both well tolerated in this study. There were no serious adverse events and no withdrawals because of an adverse event. Approximately 20% of the subjects reported an adverse event for both drugs, of which the most prevalent was sedation. Peak sedation generally occurred between 2 and 3 hours after dosing and was more prevalent in the youngest age group (2 to 5 years of age). Depth of sedation appeared to be greater for chlorpheniramine, with 2 subjects deeply sedated, whereas no subject was deeply sedated with brompheniramine. Central nervous system excitation and airway restriction were not reported as an adverse event in any subject with either drug. In addition, no clinically significant change was observed in vital signs for either drug. That the incidence of sedation was the most common side effect is consistent with the side effect profiles for both brompheniramine and chlorpheniramine.[20] A conclusive evaluation of the sedation potential of these drugs in this study population could not be undertaken because of the absence of a control group.

Study Limitations

In this study, sedation was assessed using the University of Michigan Sedation Scale (UMSS). Although the scale is validated and a study nurse took all measurements, no training was provided on the use of the scale, which may have increased the variability associated with this measurement. In addition, no placebo group was included in this study such that the effect solely from to the drug could not be estimated (ie, versus time effects, etc.).

Chlorpheniramine's metabolic pathways include CYP2D6, which is polymorphic.[12] In poor metabolizers, there is a 50% increase in AUC. In this study, no genotype or phenotype assessments were performed. Although the usual increase in CL_o with age and BW was observed, the inclusion of a term for metabolic status in the model may have allowed one to assess whether the effect for age (maturation) was the same for both poor and extensive metabolizers.

Conclusions

In conclusion, the age-/weight-based dosing nomogram for brompheniramine maleate and chlorpheniramine maleate using a 4-fold range of doses over ages 2 to 17 years achieved similar peak plasma concentrations across the pediatric cohort evaluated in these studies. Area under the plasma concentration–time profile appeared to increase slightly (~15% to 30% higher in the 12- to 17-year-old age group). For both drugs, oral clearance and the terminal volume of distribution increased with age. However, once these parameters were allometrically adjusted, no age-related differences were observed, indicating no age-related (ie, maturation) changes within this population. Both treatments were well tolerated; the most prevalent AEs were those of sedation. There were no serious AEs and no dropouts because of AEs. Based on these results, the age/weight dosing nomogram used in these studies achieved similar systemic exposures (within 15% to 30%) and would be appropriate to use in subsequent pediatric studies in which similar exposure across ages is desired.

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Declaration of Conflicting Interests

S.P., S.J., and S.M. are current or former employees of Pfizer Consumer Healthcare and have stock and/or stock options. G.A.T. is a paid consultant to Pfizer Consumer Healthcare.

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