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Guaifenesin Pharmacokinetics Following Single-Dose Oral Administration in Children Aged 2 to 17 Years

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Abstract

This study characterized guaifenesin pharmacokinetics in children aged 2 to 17 years (n = 40) who received a single oral dose of guaifenesin (age-based doses of 100-400 mg) 2 hours after breakfast. Plasma samples were obtained before and for 8 hours after dosing and analyzed for guaifenesin using liquid chromatography-tandem mass spectrometry. Pharmacokinetic parameters were estimated using noncompartmental methods, relationships with age were assessed using linear regression, and dose proportionality was assessed on 95% confidence intervals. Based on the upper dose recommended in the monograph (for both children and adolescents), area under the curve from time zero to infinity and maximum plasma concentration both increased with age. However, when comparing the upper dose for children aged 2 to 11 years with the lower dose for adolescents aged 12 to 17 years, similar systemic exposure was observed. As expected due to increasing body size, oral clearance (CL_o) and terminal volume of distribution (V_z/F) increased with age. Due to a larger increase in V_z/F than CL_o, an increase in terminal exponential half-life was also observed. Allometric scaling indicated no maturation-related changes in CL_o and V_z/F.

Keywords

guaifenesin, pharmacokinetics, dose proportionality, pediatrics

Guaifenesin (3-[2-methoxyphenoxy]-1,2-propanediol; glyceryl guaiacolate), an expectorant that increases the volume and decreases the viscosity of airway secretions and has been shown to decrease cough reflex sensitivity, is the only FDA-approved nonprescription expectorant.[1]

Guaifenesin pharmacokinetics has been assessed following single and multiple dosing in adults. Following single-dose oral administration of an immediate-release formulation, peak plasma concentrations were observed at ~0.7 hours, and the terminal exponential half-life ($t_{1/2,z}$) was ~0.8 hours.[2] Over the range of 600 to 1200 mg, the maximum plasma concentration (C_{max}) and area under the curve from time zero to infinity (AUC) appeared to increase in proportion to dose. Following multiple-dose oral administration of an immediate-release formulation, steady-state appeared to be rapidly achieved (by the time of the first postdose observation period), consistent with a short ($t_{1/2,z}$) and with a steady-state fluctuation index of ~3 ($[C_{max} - C_{min}]/C_{avg}$ where C_{min} is the trough concentration at the end of the dosing interval and C_{avg} is the average concentration over a dosing interval).[3,4] Following oral administration, guaifenesin is primarily metabolized, with β-(2-methoxyphenoxy)lactic acid as the major urinary metabolite.[5]

Historically, dosing in pediatric patients has been empirically based on body weight and/or age, since pharmacokinetic and pharmacodynamic data have generally been unavailable. The current dose recommended in the FDA-OTC monograph labeling for cold, cough, allergy, bronchodilator, and anti-asthmatic drugs indicates children 12 years and above be administered the adult dose, children 6 to <12 years of age be administered half the adult dose, and children <6 years of age be administered one quarter the adult dose. A physician should be consulted for dosing in children <2 years of age.[6] For guaifenesin, this results in a dosing regimen of 50-100 mg for 2- to 5-year-olds, 100-200 mg

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for 6- to 11-year-olds, and 200-400 mg for those aged 12 years old and above, administered every 4 hours. More recently, the product label restricted OTC use of guaifenesin in children <4 years of age.

The primary purpose of this study was to determine if the age-based dosing rule in the FDA-OTC monograph for guaifenesin achieves similar systemic exposure (C_{max} and AUC) over the range of 2 to 17 years of age. In addition, dose proportionality and relationships between guaifenesin pharmacokinetic parameters (oral clearance [CL_o], terminal volume of distribution [V_z/F] uncorrected for bioavailability and $t_{1/2,z}$) and age were assessed.

Methods

Study Design

Two separate studies were conducted in children. Both studies were reviewed by Compass Institutional Review Board (IRB) (Mesa, Arizona). To participate in either study, parent(s) or legally authorized representative(s) signed and dated an IRB-approved informed consent form, and children aged 6 years and older who were able to read, signed and dated an IRB-approved assent form. The first study was conducted in children 2 to 11 years of age. The second study included adolescents 12 to 17 years of age. Both studies used the same investigational site and a very similar study design. In subjects 2 to 11 years of age, the study was conducted as a single-dose, open-label, single-center study. In subjects 12 to 17 years of age, the study was a 2-period, single-dose, randomized crossover, open-label, single-center study.

The study populations consisted of male and female children either with symptoms associated with an upper respiratory tract infection (2 to 11 years) or at risk of an upper respiratory tract infection (2 to 17 years). Subjects were nonsmoking, healthy children and adolescents, aged 2 to 17 years, with a minimum weight of 10.9 kg and a body weight greater than the 5th and less than the 95th percentile for weight, based on age and sex.[7] Key exclusion criteria included febrile illness greater than 100°F within 7 days prior to dosing (2 to 11 years age group), positive urine pregnancy test for postmenarchal females, history of alcohol or drug abuse, and reported use of nonprescription drugs or prescription drugs except for low-dose contraceptives, vitamins, and/or fluoride supplements within 5 half-lives prior to dosing. Approximately 40 children were to be enrolled with the goal of approximately 2 children at each age and with adequate representation of males and females.

Study Conduct

Subjects 2 to 11 years of age arrived at the clinical site the morning of dosing. Subjects 12 to 17 years of age arrived at the clinical site the night prior to dosing. Subjects fasted overnight and were permitted to eat a light meal (eg, toast and/or yogurt and clear liquids) 2 hours prior to dosing. No water/fluids were permitted for 1 hour prior to dosing. Subjects were allowed clear liquids or fruit juice (other than grapefruit) 2 hours after dosing but otherwise continued to fast until 3 hours after dosing. Subjects were discharged from the site following the collection of the 8-hour blood sample. For subjects 12 to 17 years of age, the washout period between guaifenesin doses was extended to 7 days.

Drug Administration

A single dose of guaifenesin solution (100 mg/5 mL) based on age was administered by oral syringe as follows: 5 mL (100 mg) for 2- to 5-year-olds, 10 mL (200 mg) for 6- to 11-year-olds, and 10 or 20 mL (200 or 400 mg) for 12- to 17-year olds.

The above doses were only based on the upper range of doses for children 2 to 11 years of age and both the lower (200 mg) and upper (400 mg) range of dosing recommended for adolescents 12 to 17 years of age and adults in the guaifenesin FDA-OTC monograph.

Subjects drank 60 to 120 mL (2 to 11 years of age) or 240 mL (12 to 17 years of age) of water or decaffeinated beverages (eg, Sprite® or ginger ale) after swallowing the dose. Subjects were required to be administered and swallow the complete dose to continue in the study.

Other food/beverage restrictions included in children 2 to 11 years of age were xanthine/caffeine 24 hours prior to and through completion of the study, grapefruit or grapefruit juice 14 days prior to and through completion of the study, and fruit juice while in the clinic. In adolescents 12 to 17 years of age, food/beverage restrictions included consumption of alcohol 48 hours prior to day 1 of each period, consumption of grapefruit, pomelo, or Seville oranges 14 days prior to dosing and through completion of the study, and consumption of xanthine/caffeine during confinement.

Blood Sampling

Blood (1.5 mL) was collected prior to and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing. Plasma (sodium heparin) was harvested and stored at –20º C until assayed.

Safety Monitoring

Safety was evaluated based on clinical observations and assessment of adverse events (AEs), subjective symptoms and complaints, and vital signs (temperature, respiratory rate, heart rate, and blood pressure). In children 2 to 11 years of age, vital signs were obtained prior to and at 0.25, 2, 4, and 8 hours after dosing, and a physical examination was conducted pre- and postdose. In adolescents 12 to 17 years of age, vital signs

were obtained the night prior to dosing, prior to and at 8 hours after dosing, and a physical examination was conducted the night prior to dosing and at the end of the study.

Sample Assay

Guaifenesin plasma concentrations were determined using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Guaifenesin and internal standard were extracted using an organic solvent, evaporated, and subjected to LC-MS/MS. 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 2 to 2000 ng/mL, based on a 0.075 mL plasma sample. Based on QC samples run during validation (2 to 1500 ng/mL), interday variability (coefficient of variation) was 9.3% or less, and interday accuracy ranged from –3.87% to 2.24%. For QC samples (6 to 1500 ng/mL) run during the study sample assays, interday variability was 8.45% or less, interday accuracy ranged from –2.96% to 7.71% for samples obtained from children 2 to 11 years of age, interday variability was 5.03% or less, and interday accuracy ranged from –2.36% to 6.20% for samples obtained from adolescents 12 to 17 years of age. During assay development, sample stability was determined to be 92 days; all samples were analyzed within 92 days of collection.

Pharmacokinetic Analysis

Individual guaifenesin plasma concentration-time profiles were analyzed using noncompartmental analysis.[8,9] The maximum plasma concentration (C_{max}) and the time at which the maximum occurred (t_{max}) were determined based on visual inspection of individual guaifenesin 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 ($t_{1/2,z}$) 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 ($t_{1/2,z}$). Area under the plasma concentration-time profile from time 0 to infinity (AUC) was the sum of AUC_{tlast} and AUC_{ext}. Oral clearance (CL_o) and terminal volume of distribution (V_z/F) (uncorrected for bioavailability) were determined as Dose/AUC and CL_o/λ_z, respectively. In addition, CL_o and V_z/F were allometrically scaled based on the approach as outlined by Anderson and Holford (ie, $CL_{o,\,scaled} = CL_o/[(BW/70\ kg)^{3/4}]$; $V_z/F_{\,scaled} = [V_z/F]/kg$).[10] Data analyses were performed using WinNonlin v5.1.1 and SAS v9.1.3.

Statistical Analysis

The relationships between various pharmacokinetic parameters (C_{max}, AUC, CL_o, $CL_{o,scaled}$, V_z/F, and V_z/F_{scaled}) 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. An age-related change was concluded if the *P*-value associated with the slope was $<.05$ for a 2-sided test. If a significant relationship was observed for any parameter with age, the magnitude of change was estimated using the predicted values. Dose proportionality and dose independence were assessed using a 1-way analysis of variance (ANOVA). If the 95% confidence interval for the ratio of geometric means (400 mg/200 mg) included 2 for dose-related parameters and 1 for dose-independent parameters, dose proportionality was concluded for each individual parameter.

Results

Subject Demographics

Forty subjects were enrolled, and all subjects completed the study. One subject was excluded from the pharmacokinetic analysis since a portion of the dose was spilled during dosing (age group: 6 to 11 years). Demographics for subjects enrolled in the study are summarized in Table 1.

For each age group, 2 or more subjects were enrolled except for ages 7 and 17 years (n = 1). The majority of subjects were African-American (n = 34) with a similar number of males and females (n = 18 and 22, respectively). As expected, body weight increased on average with age.

Guaifenesin Exposure/Pharmacokinetics

Guaifenesin 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 to 5, 6 to 11, and 12 to 17 years). Because adolescents 12 to 17 years of age were administered 2 different doses, the relationship between systemic exposure (C_{max} and AUC) and age was assessed using either 200 mg or 400 mg along with the data obtained from children 2 to 11 years of age.

The relationships between C_{max} and AUC versus age based on the higher dose recommended in the monograph for each age group are illustrated in Figure 2, panels A and B, respectively. These results indicate a significant increase in systemic exposure with age for C_{max} and AUC (C_{max} slope *P*-value = .0288; AUC: slope *P*-value = .0008), which appears to be primarily

Table 1. Subject Demographics for Pediatric Subjects Administered a Single Oral Dose of Guaifenesin

Demographics	Age Group[a]		
	2–5 Years (n = 14)	6–11 Years (n = 14)	12–17 Years (n = 12)
Age[b] (years)			
Mean	3.3	8.7	14.3
SD[c]	1.0	1.9	1.7
Body weight[d] (kg)			
Mean	16.0	33.3	56.0
SD[c]	2.7	8.9	7.2
Height[e] (cm)			
Mean	99.7	134.4	163.9
SD[c]	9.5	12.6	7.7
Race			
African-American	11	13	10
White	3	1	1
Asian	0	0	1
Sex			
Female	6	9	7
Male	8	5	5

[a]Age categories are those listed in the guaifenesin monograph.
[b]Age is calculated age at screening.
[c]Standard deviation.
[d]Weight is obtained at admission.
[e]Height is obtained at screening.

related to higher exposure (~2-fold higher) in adolescents 12 to 17 years of age as compared to children 2 to 11 years of age. Alternatively, if one assumes that the lower adult dose is administered to children 6 to 17 years of age (200 mg) and that children aged 2 to 6 are administered half this adult dose (100 mg), the relationships between C_{max} and AUC versus age are no longer significant (Figure 2, panels C and D; C_{max} slope P-value = .45; AUC slope P-value = .83).

Since guaifenesin pharmacokinetics were generally dose proportional/linear (see section below), the average of the 2 parameter values observed in the 12- to 17-year-old subjects following 200 mg and 400 mg was used for assessing the influence of age on guaifenesin pharmacokinetic parameters. Guaifenesin median time to peak concentration (t_{max}) was the same across all age groups (Table 2; t_{max} = 0.5 hours). The relationships between oral clearance and the terminal volume of distribution with age are illustrated in Figure 3.

Observed oral clearance increased with age (Figure 3, panel A; slope P-value < .0001); over the range of 2 to 17 years, oral clearance increased ~150% (56.0 to 140 L/h). However, following allometric adjustment, oral clearance normalized to 70 kg was no longer significantly related to age (ie, P-value = .0981; Figure 3, panel B).

The observed terminal volume of distribution, unadjusted for bioavailability, also increased with age (Figure 3, panel C; slope P-value < .0001); over the range of 2 to 17 years, the terminal volume of distribution increased ~515% (32.9 to 203 L, respectively). However, following allometric adjustment, the terminal volume of distribution was no longer significantly related to age (Figure 3, panel D; slope P-value = .6769).

The relationship between the $t_{1/2,z}$ and age is also illustrated in Figure 3 (panel E). Although the $t_{1/2,z}$ was short across all age groups (~1 hour or less), it did show a statistically significant increase with age ($t_{1/2,z}$: slope P-value < .0001); over the range of 2 to 17 years of age, $t_{1/2,z}$ increased ~85% (0.557 to 1.04 hours).

Dose Proportionality

In the adolescent group, randomized single doses of 200 mg and 400 mg were orally administered. The comparison of these parameters for dose proportionality/dose independence based on individual ratios is summarized in Table 2 (400 mg/200 mg ratio and corresponding 95% confidence interval). All parameters were dose proportional/dose independence except for the $t_{1/2,z}$. For this parameter, a very small (~6%) but statistically significant decrease was noted following 400 mg.

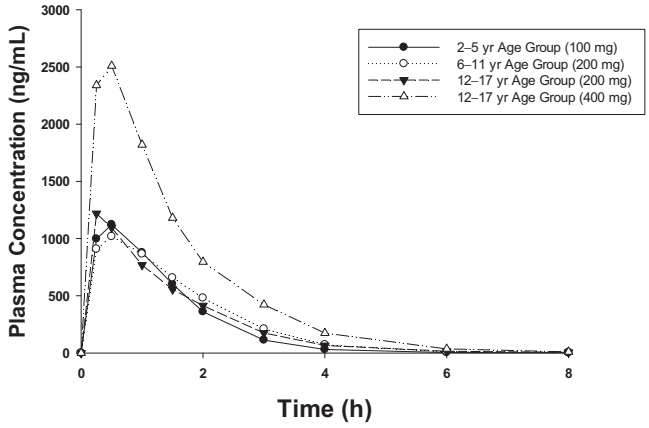

Figure 1. Mean guaifenesin plasma concentration-time profiles summarized by age group and dose following single-dose oral administration.

Table 2. Geometric Mean (CV%) Guaifenesin Pharmacokinetics Summarized by Age Group and Dose Following Single-Dose Oral Administration

	Age Group			
PK Parameter	2–5 Years (n = 14)	6–11 Years (n = 13)	12–17 Years (n = 12)	
Dose	100 mg	200 mg	200 mg	400 mg
C_{max} (ng/mL)	1173 (55.2)	1082 (44.6)	1085 (79.4)	2316 (73.8)
			2.13 (95%CI: 1.41 to 3.23)[b]	
T_{max}[a] (hours)	0.5 (0.25, 1.5)	0.5 (0.25, 1.0)	0.5 (0.25, 1.0)	0.5 (0.25, 1.5)
			1.11 (95%CI: 0.714 to 1.72)	
AUC (ng · h/mL)	1728 (40.2)	1990 (30.7)	1902[c] (49.5)	4062 (48.4)
			2.19 (95%CI: 1.74 to 2.75)	
CL_o (L/h)	57.9 (40.2)	100.5 (30.7)	105.2[c] (49.5)	98.46 (48.4)
			0.915 (95%CI: 0.728 to 1.15)	
$CL_{o,scaled}$ (L/h; normalized to 70 kg)	177.9 (35.9)	182.0 (22.7)	124.5[c] (44.1)	116.4 (44.1)
			0.919 (95%CI: 0.732 to 1.15)	
V_z/F (L)	50.07 (30.2)	103.0 (28.0)	156.8[c] (62.0)	135.7 (56.3)
			0.858 (95%CI: 0.675 to 1.09)	
V_z/F_{scaled} (L/kg)	3.2 (25.0)	3.2 (15.2)	2.8[c] (53.1)	2.4 (50.4)
			0.862 (95%CI: 0.679 to 1.09)	
$t_{1/2,z}$ (hours)	0.6 (18.6)	0.7 (17.9)	1.03[c] (15.8)	0.96 (13.1)
			0.940 (95%CI: 0.900 to 0.982)	

[a]Median (min, max) shown for t_{max}.
[b]Geometric mean of individual parameter ratios (400 mg/200 mg) and associated 95% confidence interval.
[c]n = 11.

Safety Results

No serious AEs or withdrawals due to AEs occurred during the study. In children 2 to 11 years of age, no AEs were observed and no clinically significant changes in vital signs were reported. In addition, no postdose changes were documented for the physical exam. In adolescents 12 to 17 years of age, no AEs associated with vital signs were observed. Two treatment-emergent AEs (dyspepsia, mild severity; gastroenteritis, moderate severity) were reported in 1 subject following a 400-mg dose. Both events were considered by the investigator as unrelated to the study drug and resolved without complications.

Discussion

This study characterized guaifenesin pharmacokinetics in children 2 to 17 years of age following single-dose oral administration of an age-based dose using a guaifenesin solution (100 mg to 400 mg).

The current guaifenesin FDA-OTC monograph recommends that children 2 to 5 years of age be administered one quarter the adult dose, children 6 to 11 years of age be administered half the adult dose, and children 12 years or older be administered the adult dose. This study showed higher systemic exposure for subjects aged 12 to 17 years taking the higher monograph dose recommended for adolescents and adults (400 mg) than subjects aged 2 to 11 years taking the higher dose recommended for children (100 mg in children aged 2 to 5 years and 200 mg in children aged 6 to 11 years). When children 6 to 17 years of age were administered a 200-mg dose (the lower monograph dose recommended for adults and adolescents 12 to 17 years of age and the upper monograph dose for children 6 to 11 years of age) and children 2 to 5 years of age were administered half this dose (upper monograph dose), no age-related differences for AUC and C_{max} were observed. These findings suggest that if guaifenesin exposure is dose proportional in 2- to 11-year-old children as was observed in adolescents, the lower dose recommended for children (50 mg in children aged 2 to 5 years and 100 mg in children aged 6 to 11 years) may result in lower systemic exposures in children 2 to 11 years of age as compared to adolescents 12 to 17 years of age. However, because the exposure-response relationship is not established, the clinical importance of these findings remains to be determined.

As expected, due to increasing body weight, oral clearance and terminal volume of distribution increased significantly with age. However, when oral clearance and terminal volume of distribution were allometrically scaled as recommended by Anderson and Holford,[10] no statistically significant age-related change was observed. Because $t_{1/2,z}$ is dependent on both V_z/F and CL_o ($t_{1/2,z} = 0.693\ [V_z/F]/CL_o$) and the terminal volume of distribution had a larger increase with age than oral clearance, there was also a significant increase in the $t_{1/2,z}$ with age. However, the difference in the $t_{1/2,z}$ is not expected to be clinically important because it is ~1 hour or less and the drug is administered every 4 hours.

When the results from this study are compared to those previously reported for adults, good agreement is generally observed. In children, peak plasma

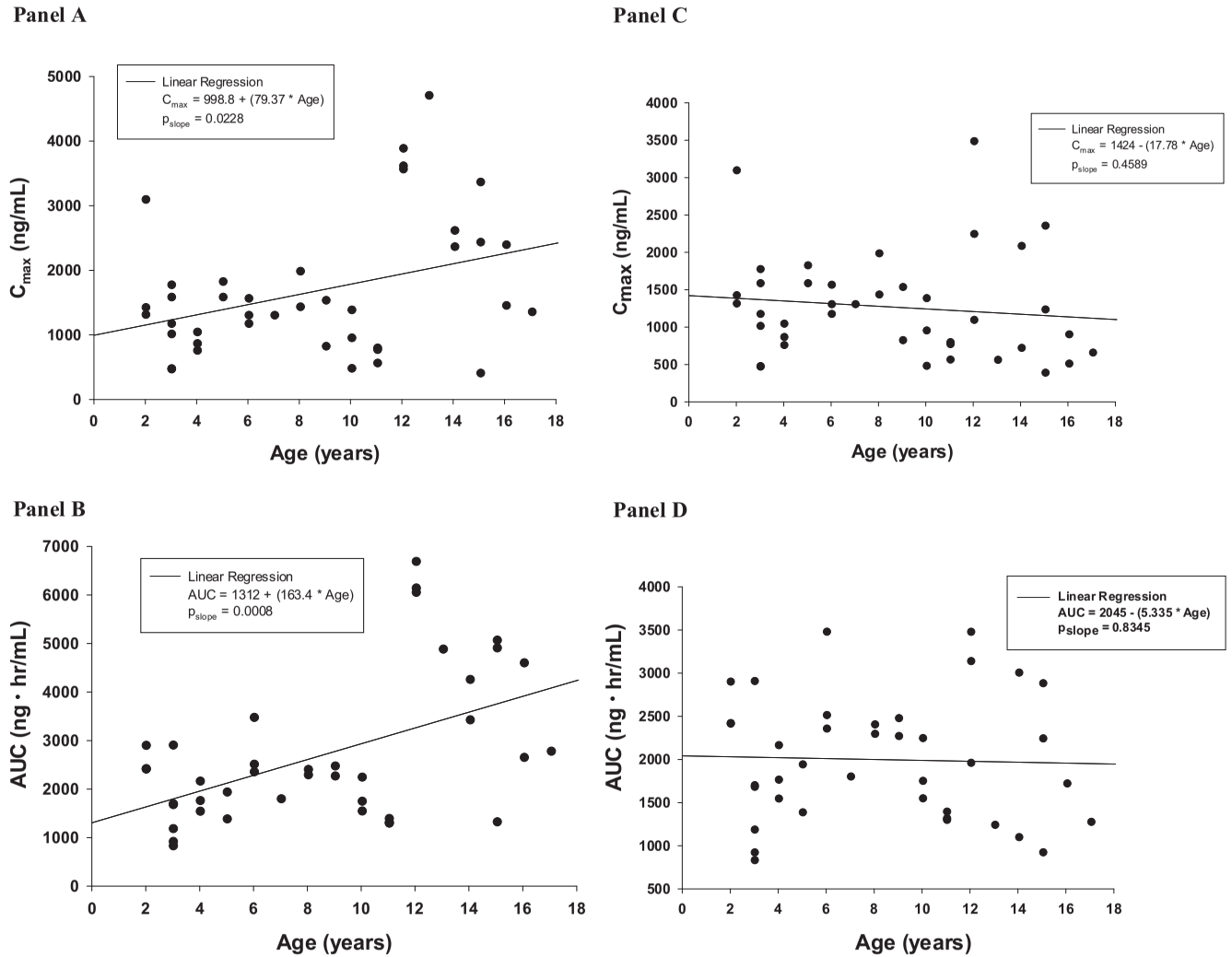

Figure 2. The relationships between guaifenesin peak plasma concentration (C_{max}; panels A and C) or area under the plasma concentration-time profile (AUC; panels B and D) and age following single-dose oral administration. Panels A and B use adolescent data following 400 mg; panels C and D use adolescent data following 200 mg.

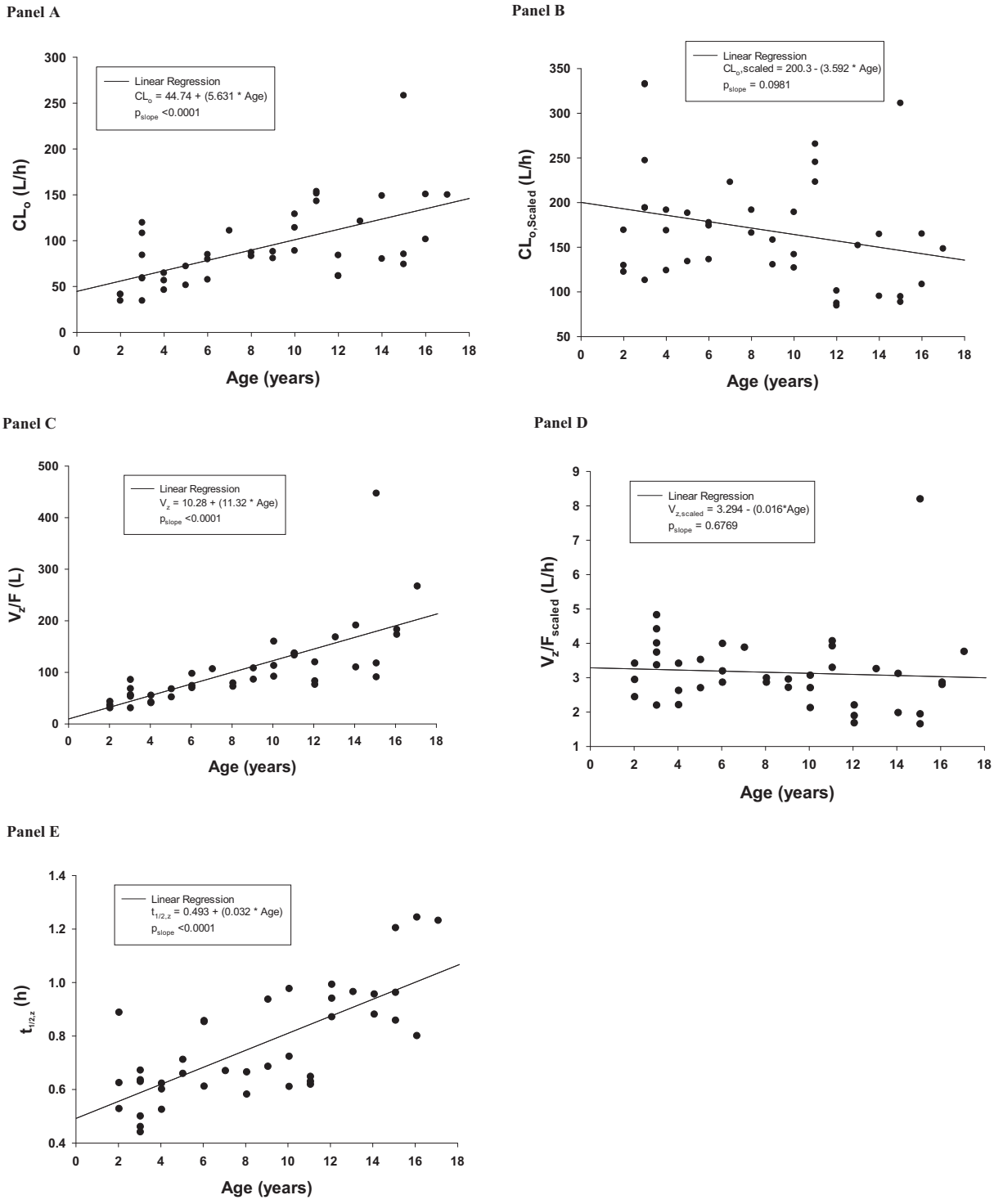

Figure 3. The relationships between guaifenesin oral clearance (CL_o; panel A), allometrically scaled oral clearance ($CL_{o,scaled}$; panel B), terminal volume of distribution (V_z/F; panel C), allometrically scaled terminal volume of distribution (V_z/F_{scaled}; panel D), or terminal exponential half-life ($t_{1/2,z}$; panel E) and age following single-dose oral administration.

concentrations occurred at 0.5 hour, which is similar to that reported in adults (0.25 to 0.7 hour).[2,11,12] The $t_{1/2,z}$ in children increased with age (0.6 to 1 hours) but was similar to that reported in adults (0.8 to 1.0 hours).[2,11,12] In addition, dose-adjusted systemic exposure in adolescents 12 to 17 years of age was also similar to adults (adolescents following 400 mg: C_{max} = 2316 ng/mL, AUC = 4062 ng · h/mL; adults following

600 mg: $C_{max} = 3177$ ng/mL, AUC = 4905 ng · h/mL (ie, dose-adjusted C_{max} and AUC were 8% and 19% lower in adults, respectively).

In conclusion, results from this study indicated that the current FDA-OTC monograph recommendations for guaifenesin may result in lower systemic exposure in children 2 to 11 years of age as compared to adolescents 12 to 17 years of age; the clinical significance of this finding remains to be determined. As expected, oral clearance and the apparent terminal volume of distribution increase with age; however, following allometric adjustment, no age-related (ie, maturation) change is observed. Systemic exposures associated with 200 mg and 400 mg appear to increase in proportion to dose. All treatments were well tolerated, and no serious AEs and no drop-outs due to AEs were reported.

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