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Pharmacokinetics of a Guanfacine Extended-Release Formulation in Children and Adolescents with Attention-Deficit–Hyperactivity Disorder

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Study Objective. To evaluate the single- and multiple-dose pharmacokinetics of an oral extended-release formulation of guanfacine in children and adolescents with a diagnosis of attention-deficit–hyperactivity disorder (ADHD).

Design. Phase I-II, open-label, dose-escalation study.

Setting. Clinical study center.

Patients. Fourteen children (aged 6–12 yrs) and 14 adolescents (aged 13–17 yrs) with ADHD.

Intervention. All patients received guanfacine as a single 2-mg dose on day 1. They received a daily dose of 2 mg on days 9–15, 3 mg on days 16–22, and 4 mg on days 23–29.

Measurements and Main Results. Blood samples, vital signs, and electrocardiograms (ECGs) were obtained before dosing on day 1 and at intervals over 24 hours, with repeat measurements on days 14 and 28. Guanfacine demonstrated linear pharmacokinetics. Mean plasma concentrations, peak exposure (C_{max}), and total or 24-hour exposure (area under the concentration-time curve $[AUC]_{0-\infty}$ or AUC_{0-24}, respectively) were as follows in children and adolescents, respectively: after a single 2-mg dose, $AUC_{0-\infty}$ was 65.2 ± 23.9 ng•hour/ml and 47.3 ± 13.7 ng•hour/ml, and C_{max} was 2.55 ± 1.03 ng/ml and 1.69 ± 0.43 ng/ml; after multiple 2-mg doses, AUC_{0-24} was 70.0 ± 28.3 ng•hour/ml and 48.2 ± 16.1 ng•hour/ml, and C_{max} was 4.39 ± 1.66 ng/ml and 2.86 ± 0.77 ng/ml; and after multiple 4-mg doses, AUC_{0-24} was 162 ± 116 ng•hour/ml and 117 ± 28.4 ng•hour/ml, and C_{max} was 10.1 ± 7.09 ng/ml and 7.01 ± 1.53 ng/ml. After a single 2-mg dose, half-life was 14.4 ± 2.39 hours in children and 17.9 ± 5.77 hours in adolescents. The most frequent treatment-emergent adverse events were somnolence, insomnia, headache, blurred vision, and altered mood. Most were mild to moderate in severity, with the highest frequency associated with the 4-mg doses. Blood pressure, pulse, and ECG readings were all within normal limits.

Conclusion. Guanfacine extended-release formulation demonstrated linear pharmacokinetics. Plasma concentrations and concentration-related pharmacokinetic parameters were higher in children than in adolescents. These differences are likely due to heavier body weights in adolescents and young male subjects. No serious adverse events were reported.

Key Words: attention-deficit–hyperactivity disorder, ADHD, guanfacine, SPD503, extended release, pharmacokinetics, children, adolescents, nonstimulant, stimulant.

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In recent years, the treatment of attention-deficit–hyperactivity disorder (ADHD) with α_2-adrenoreceptor agonists, such as guanfacine and clonidine, has steadily increased.[1, 2] The formulations used for this disorder have been immediate-release guanfacine and clonidine tablets and a clonidine transdermal therapeutic system, all previously approved and marketed for the treatment of hypertension.

Preliminary evidence exists in humans to demonstrate the beneficial effects of α_2-agonists in the treatment of ADHD.[3–7] Through animal models, the mechanism by which α_2-agonists benefit patients with ADHD appears to involve postsynaptic agonism of α_2-receptors in the prefrontal cortex. In studies involving monkeys, stimulation of the postsynaptic prefrontal cortex α_2-receptors by guanfacine improved performance on cognitive tasks,[8] clonidine increased the working memory of monkeys performing spatial working memory tasks,[9] and the systemic administration of guanfacine increased regional blood flow to parts of the monkey prefrontal cortex considered responsible for spatial working memory.[10] Several studies have indicated that the receptor underlying the benefits of α_2-agonists is the α_{2A} subtype.[11–13] Guanfacine acts selectively at α_{2A}-receptors in the cerebral cortex,[14, 15] whereas clonidine has affinity for all α_2-receptors, including α_{2B}, as well as α_1, β-adrenergic, histaminergic, and possibly dopaminergic receptors.[4, 14, 15]

As reported in the literature, the use of guanfacine immediate-release formulation in the treatment of ADHD is limited by its short duration of action and need for multiple daily doses (2–4 times/day).[3, 5, 7] As a result, a new extended-release tablet formulation of guanfacine is under investigation for the treatment of ADHD. Intended for once-daily oral administration, this formulation consists of guanfacine hydrochloride in a matrix tablet containing functional excipients that, after oral administration, control and extend release of the drug throughout the gastrointestinal tract.

The primary objective of this study was to determine the pharmacokinetics of guanfacine extended release after a single dose of 2 mg and multiple doses of 2–4 mg. Additional objectives were to assess the effect of guanfacine extended release pharmacokinetics on demographic subgroups, and to evaluate the relationship between guanfacine extended release plasma concentrations with vital sign measurements and electrocardiograms (ECGs).

Methods

This study was a phase I-II, open-label, dose-escalation, pharmacokinetic evaluation of guanfacine extended-release tablets (2, 3, and 4 mg) in children and adolescents with a diagnosis of ADHD. The study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989), and 48th (Somerset West [South Africa] 1996) World Medical Assemblies. The study also conformed to the Declaration of Helsinki (2000) and the International Conference on Harmonisation Guideline for Good Clinical Practice (1996). The study protocol was approved by the Arkansas Institutional Review Board. Before performance of any related procedures, written informed consent and assent were obtained from each of the subjects and their parents or legally authorized representatives after a thorough explanation and discussion of the study with the principal investigator.

Subjects

Subjects were recruited from a database of more than 500 children and adolescents with ADHD who had previously indicated an interest in taking a nonstimulant drug. Since this was a pharmacokinetic study, many subjects and their parents decided to participate for altruistic reasons. Families were also compensated for time spent at the study center.

The subjects consisted of boys and girls aged 6–17 years, divided into children aged 6–12 years and adolescents aged 13–17 years. The diagnosis of ADHD was based on a detailed psychiatric evaluation according to ADHD criteria in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*.[16] All subjects were required to have an age-appropriate intellectual level; blood pressure within the 95th

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percentile for age, sex, and height; and a normal ECG. Subjects with a specific cardiac condition or family history of significant cardiac condition were excluded. Girls of child-bearing potential were required to have a negative pregnancy test at screening and at each check-in.

Study Design

After a prestudy screen, subjects entered a washout period. The washout of prior drugs began at 1 week for over-the-counter and ADHD drugs and at 2 weeks for most prescription drugs (excluding ADHD drugs and hormonal contraceptives); for prescription drugs with half-lives longer than 2 weeks, the washout was a period equal to 5 times the half-life.

Doses of guanfacine were administered at approximately 7:00 A.M. throughout the study. Doses generally were administered at home; however, doses were given at the clinic on days 1, 14, 15, 23, 28, and 29. On days 1, 14, and 28, the drug was given after an overnight fast.

On day 1, subjects received a single 2-mg dose of guanfacine. Venous blood samples were drawn into a sodium ethylenediaminetetraacetic acid (EDTA) vacutainer at 0 hour (before dosing) and at 1, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 48, 72, and 96 hours after dosing.

Subjects then received a daily dose of 2 mg on days 9–15, 3 mg on days 16–22, and 4 mg on days 23–29. Dosing compliance was verified by drug accountability and parent report. Blood samples were taken at 0 hour (before dosing) and at 1, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours after dosing on days 14 and 28. An additional blood sample was taken on day 23 to assess 3-mg dose trough concentrations. In all subjects, guanfacine extended release was discontinued by dose titration in 1-mg decrements starting on day 30.

On day 37, 2 days after discontinuation of guanfacine extended release, subjects returned to the clinic for an end-of-study assessment. Subjects were monitored for 30 days after discontinuation to document any ongoing adverse events. A schematic of the dosing regimen is presented in Figure 1.

Bioanalytic Assays

Plasma guanfacine concentrations were determined by using a validated liquid chromatography with tandem mass spectrometry detection method. The lower and upper limits of quantitation for guanfacine in EDTA plasma were 0.05 and 25.0 ng/ml, respectively. The in-study accuracy and precision of the clinical samples received for analysis were monitored by the simultaneous assay of quality control samples along with the clinical samples. The mean percent accuracies of the calibration standards were between 96.8% and 103.1%, and the precision ranged from 2.4–5.5%. The quality control samples showed mean percent accuracies of 98.0–104.5%, with precision ranging from 4.4–8.6%.

Pharmacokinetic Assessments

The pharmacokinetic parameters included the area under the drug concentration–time curve (AUC) from time zero to the last time point with a measurable concentration (AUC_{0-t} [e.g., AUC_{0-24}]), the AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$), the elimination half-life, the maximum concentration (C_{max}), the time to C_{max} (T_{max}), the terminal elimination rate constant (λ_z), oral clearance, and the oral volume of distribution. These parameters were calculated by using noncompartmental analysis.

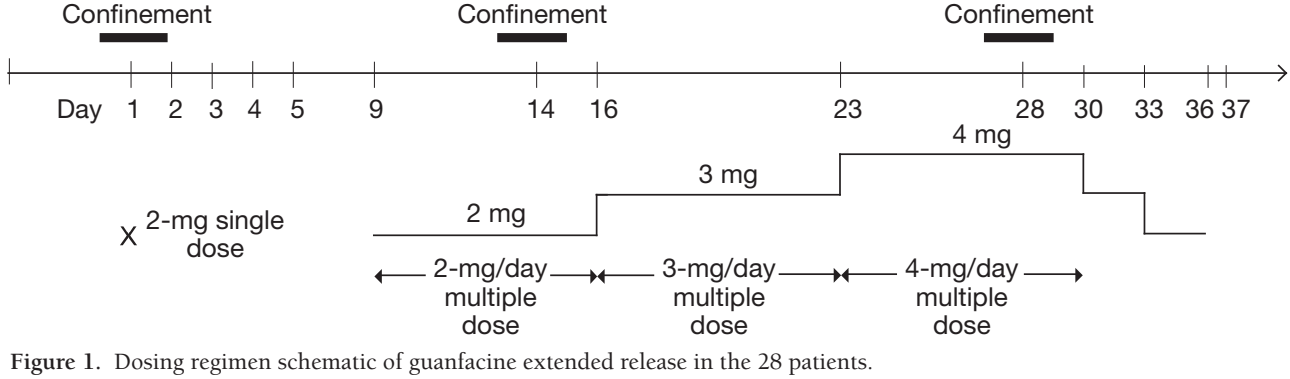

Figure 1. Dosing regimen schematic of guanfacine extended release in the 28 patients.

Table 1. Demographics of the Children and Adolescents with Attention-Deficit–Hyperactivity Disorder

Characteristic	Children (n=14)	Adolescents (n=14)	Total (n=28)
	No. (%) of Patients		
Sex			
Male	7 (50)	12 (86)	19 (68)
Female	7 (50)	2 (14)	9 (32)
Race			
Caucasian	9 (64)	12 (86)	21 (75)
African-American	4 (29)	1 (7)	5 (18)
Other	1 (7)	1 (7)	2 (7)
	Mean ± SD		
Age (yrs)	9.3 ± 1.82	14.2 ± 1.05	11.8 ± 2.90
Weight (kg)	34.7 ± 10.8	57.1 ± 9.47	45.9 ± 15.1
Height (cm)	137.9 ± 11.7	165.4 ± 9.98	151.6 ± 17.5
Body mass index (kg/m^2)	17.8 ± 2.60	20.8 ± 2.33	19.3 ± 2.85

Safety Assessments

Vital sign measurements and adverse-event assessments were performed on days 1, 2, 3, 4, 5, 13, 14, 15, 23, 27, 28, 29, and 37. The ECGs were obtained at screening and on days 0, 1, 2, 14, 15, 23, 28, 29, and 37. Laboratory assessments and physical examinations were conducted during screening and at end of study.

Statistical Analysis

The statistical analysis involved two populations: a safety population that received at least one dose of guanfacine extended release, and a pharmacokinetic population that, in addition to receiving at least one dose of the study drug, provided postdose drug concentration data.

Number of observations, arithmetic mean ± SD, coefficient of variation, median, geometric mean, minimum, and maximum were recorded and/or calculated for each pharmacokinetic parameter, as appropriate. Similar analyses were performed for predefined subgroups based on age, sex, and body weight. Subgroups by body weight were less than 34 kg, 34 to less than 50 kg, and 50 kg or more.

The relationship between pharmacokinetic statistics and cardiovascular or treatment-emergent adverse events was explored. Cardiovascular data were explored for possible relationships between pharmacokinetic statistics and changes in systolic and diastolic blood pressure, heart rate, and ECG by using graphic methods. If this analysis suggested a possible relationship, an attempt was made to fit linear and/or nonlinear models to the data. Treatment-

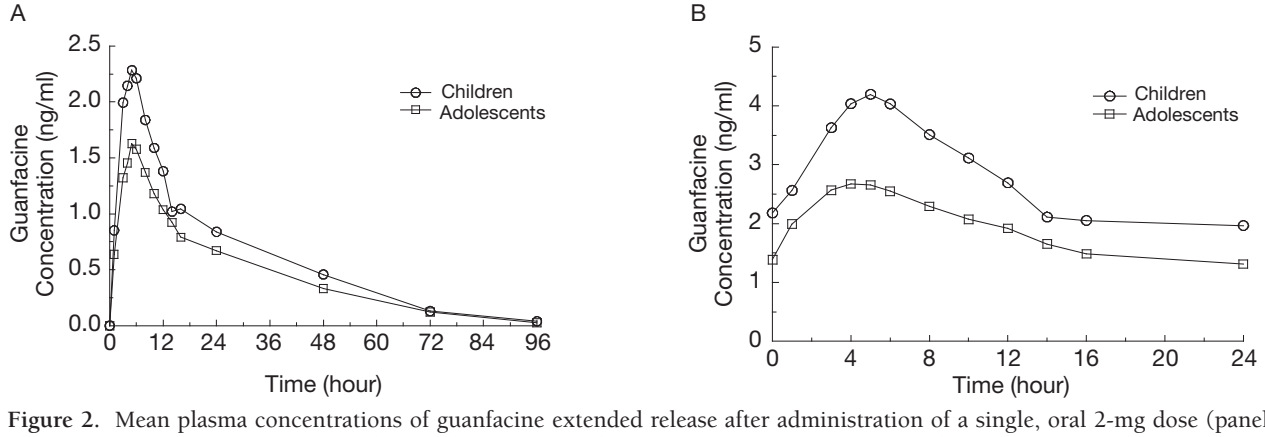

Figure 2. Mean plasma concentrations of guanfacine extended release after administration of a single, oral 2-mg dose (panel A) and multiple, 2-mg daily doses (panel B) to children (aged 6–12 yrs) and adolescents (aged 13–17 yrs) with attention-deficit–hyperactivity disorder.

Table 2. Summary of Pharmacokinetic Parameters of a Guanfacine Extended-Release Formulation After Administration of a 2-mg Single Oral Dose

Parameter	Children Aged 6–12 Years (n=14)	Adolescents Aged 13–17 Years (n=14)
	Median (range)	
T_{max} (hrs)	4.98 (2.93–8.43)	4.96 (3.97–6.00)
	Mean ± SD	
C_{max} (ng/ml)	2.6 ± 1.03	1.7 ± 0.43
AUC_{0-t} (ng•hr/ml)	56.9 ± 22.05	42.7 ± 12.85
	(n=9)[a]	(n=12)[a]
$AUC_{0-\infty}$ (ng•hr/ml)	65.2 ± 23.88	47.3 ± 13.69
λ_z (hr^{-1})	0.0496 ± 0.0093	0.0428 ± 0.0153
Half-life (hrs)	14.4 ± 2.39	17.9 ± 5.77
Oral clearance		
Unadjusted (ml/min)	578 ± 215	754 ± 190
Weight-adjusted (ml/min/kg)	19.0 ± 8.08	13.3 ± 2.85
Oral volume of distribution		
Unadjusted (L)	722 ± 326	1134 ± 343
Weight-adjusted (L/kg)	23.7 ± 11.92	19.9 ± 5.42

T_{max} = time to maximum concentration; C_{max} = maximum concentration; AUC_{0-t} = area under the concentration-time curve from time zero to the last time point with a measurable concentration; $AUC_{0-\infty}$ = AUC from time zero extrapolated to infinity; λ_z = terminal elimination rate constant.

[a]Number of patients is nine for children and 12 for adolescents for $AUC_{0-\infty}$, λ_z, half-life (for consistency), oral clearance, and volume of distribution, due to lack of log-linear decay.

emergent adverse events were explored for possible relationships between parameters of systemic exposure (C_{max} and AUC_{0-t}) and treatment-emergent adverse-event intensity (mild, moderate, severe) by using Spearman correlation coefficients. Rank statistics were applied to C_{max} and AUC_{0-t}, and ranks were plotted against the greatest intensity of a particular treatment-emergent adverse event.

Observed adverse events were encoded by using the Medical Dictionary for Regulatory Activities, version 7.0 (MedDRA; Maintenance and Support Service Organization, Reston, VA). The frequency of treatment-emergent adverse events and the number of subjects experiencing adverse events were summarized by system organ class and preferred term within each treatment condition and overall. The QT interval was corrected by using Bazett's and Fredericia's correction factors (QTcB and QTcF, respectively). The severity of QTcF changes from baseline was determined by the number of subjects showing changes of 30 msec or more, less than 60 msec, or 60 msec or more.

Results

Subjects

All 28 enrolled subjects, 14 children and 14 adolescents, completed the study. The demographics are shown in Table 1. Mean ± SD age was 9.3 ± 1.82 years for children, 14.2 ± 1.05 years for adolescents, and 11.8 ± 2.90 years overall (range 7–16 years). Although boys and girls were represented equally, 12 (86%) of the 14 adolescents were male. Twenty-one (75%) of the 28 subjects were Caucasian, and 5 (18%) were African-American.

Pharmacokinetic Parameters

Administration of a single 2-mg dose of guanfacine extended release showed differences between children and adolescents (Figure 2A, Table 2). Mean values for plasma guanfacine concentrations, as well as C_{max} and $AUC_{0-\infty}$, were higher in children than in adolescents. The median T_{max} was essentially the same in both age groups and after a single 2-mg dose T_{max} was 4.98 hours in children and 4.96 hours in adolescents. The differences in oral clearance and volume of distribution between children and adolescents depended on whether the data were adjusted for weight. The unadjusted data showed oral clearance and volume of distribution to be lower in children, but weight-adjusted data showed these measures to be lower in adolescents.

Similar trends were shown in the treatment phases involving multiple 2- and 4-mg doses of the study drug. Compared with adolescents,

Table 3. Summary of Pharmacokinetic Parameters of a Guanfacine Extended-Release Formulation After Administration of 2-mg or 4-mg Multiple Doses

	2-mg Multiple Doses		4-mg Multiple Doses	
Parameter	Children Aged 6–12 Years (n=14)	Adolescents Aged 13–17 Years (n=14)	Children Aged 6–12 Years (n=14)	Adolescents Aged 13–17 Years (n=14)
	Median (range)			
T_{max} (hrs)	4.98 (3.95–7.97)	4.53 (2.93–7.98)	5.02 (3.97–10.3)	4.97 (1.00–7.97)
	Mean ± SD			
C_{max} (ng/ml)	4.4 ± 1.66	2.9 ± 0.77	10.1 ± 7.09	7.0 ± 1.53
$AUC_{0–24}$ (ng•hr/ml)	70.0 ± 28.33	48.2 ± 16.06	162.1 ± 115.56	116.7 ± 28.37
Oral clearance				
Unadjusted (ml/min)	552 ± 215	826 ± 486	522 ± 212	607 ± 166
Weight-adjusted (ml/min/kg)	15.3 ± 4.11	14.4 ± 8.34	14.3 ± 3.70	10.7 ± 3.11

T_{max} = time to maximum concentration; C_{max} = maximum concentration; $AUC_{0–24}$ = area under the concentration-time curve from time 0–24 hours.

Table 4. Summary of Pharmacokinetic Parameters of a Guanfacine Extended-Release Formulation by Dose and Body Weight

Dose	Weight[a] (kg)	$AUC_{0–t}$ (ng•hr/ml)	C_{max} (ng/ml)
Single dose, 2 mg	< 34	64.3 ± 25.4	3.10 ± 0.94
	34 to < 50	54.3 ± 15.1	1.98 ± 0.60
	≥ 50	39.6 ± 8.6	1.63 ± 0.41
Multiple dose, 2 mg	< 34	86.4 ± 25.5	5.39 ± 1.43
	34 to < 50	49.1 ± 12.5	3.07 ± 0.77
	≥ 50	47.8 ± 16.3	2.85 ± 0.76
Multiple dose, 4 mg	< 34	207.5 ± 137.6	12.97 ± 8.37
	34 to < 50	115.9 ± 9.4	7.43 ± 0.97
	≥ 50	119.7 ± 32.3	6.56 ± 1.74

$AUC_{0–t}$ = area under the concentration-time curve from time zero to the last time point with a measurable concentration; C_{max} = maximum concentration.
[a]Number of patients is eight for < 34 kg, six for 34 to < 50 kg, and 14 for ≥ 50 kg.

children had higher mean plasma guanfacine concentrations, C_{max}, and $AUC_{0–24}$ values (Figures 2B and 3, Table 3). After multiple daily 2-mg doses, the $AUC_{0–24}$ was 70.0 ± 28.3 ng•hour/ml in children and 48.2 ± 16.1 ng•hour/ml in adolescents, whereas the C_{max} was 4.39 ± 1.66 ng/ml in children and 2.86 ± 0.77 ng/ml in adolescents. Similarly, after multiple daily 4-mg doses, the $AUC_{0–t}$ was 170.1 ± 143.7 ng•hour/ml in girls and 125.0 ± 34.1 ng•hour/ml in boys, whereas the C_{max} was 10.89 ± 8.71 ng/ml in girls and 7.48 ± 2.05 ng/ml in boys. Mean C_{max} and $AUC_{0–24}$ after administration of guanfacine extended release 4 mg once/day were essentially twice those after administration of 2 mg once/day, consistent with a linear pharmacokinetic profile.

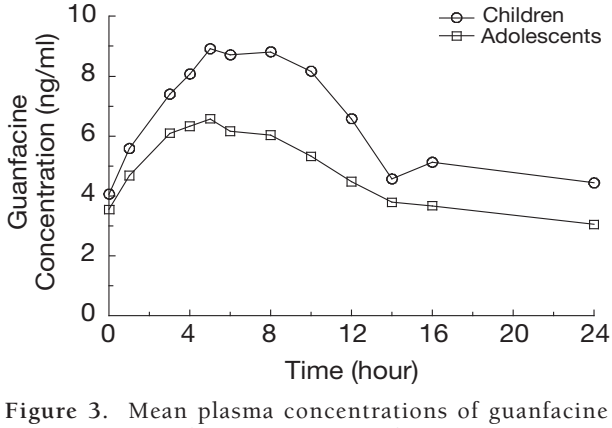

Figure 3. Mean plasma concentrations of guanfacine extended release after administration of multiple, 4-mg daily doses to children (aged 6–12 yrs) and adolescents (aged 13–17 yrs) with attention-deficit–hyperactivity disorder.

Subgroup analysis showed that an increase in body weight was associated with a definite trend toward a decrease in guanfacine C_{max} and an apparent, though not as pronounced, decrease in

Table 5. Summary of Pharmacokinetic Parameters of a Guanfacine Extended-Release Formulation by Dose and Sex

Dose	Sex	AUC_{0-t} (ng•hr/ml)	C_{max} (ng/ml)
Single dose, 2 mg	Male	49.9 ± 15.2	1.88 ± 0.75
	Female	58.0 ± 24.5	2.64 ± 0.97
Multiple dose, 2 mg	Male	54.6 ± 23.2	3.26 ± 1.25
	Female	68.7 ± 28.0	4.39 ± 1.73
Multiple dose, 4 mg	Male	124.9 ± 34.1	7.48 ± 2.05
	Female	170.1 ± 143.7	10.89 ± 8.71

AUC_{0-t} = area under the concentration-time curve from time zero to the last time point with a measurable concentration; C_{max} = maximum concentration.
Number of male subjects is 19; number of female subjects is nine.

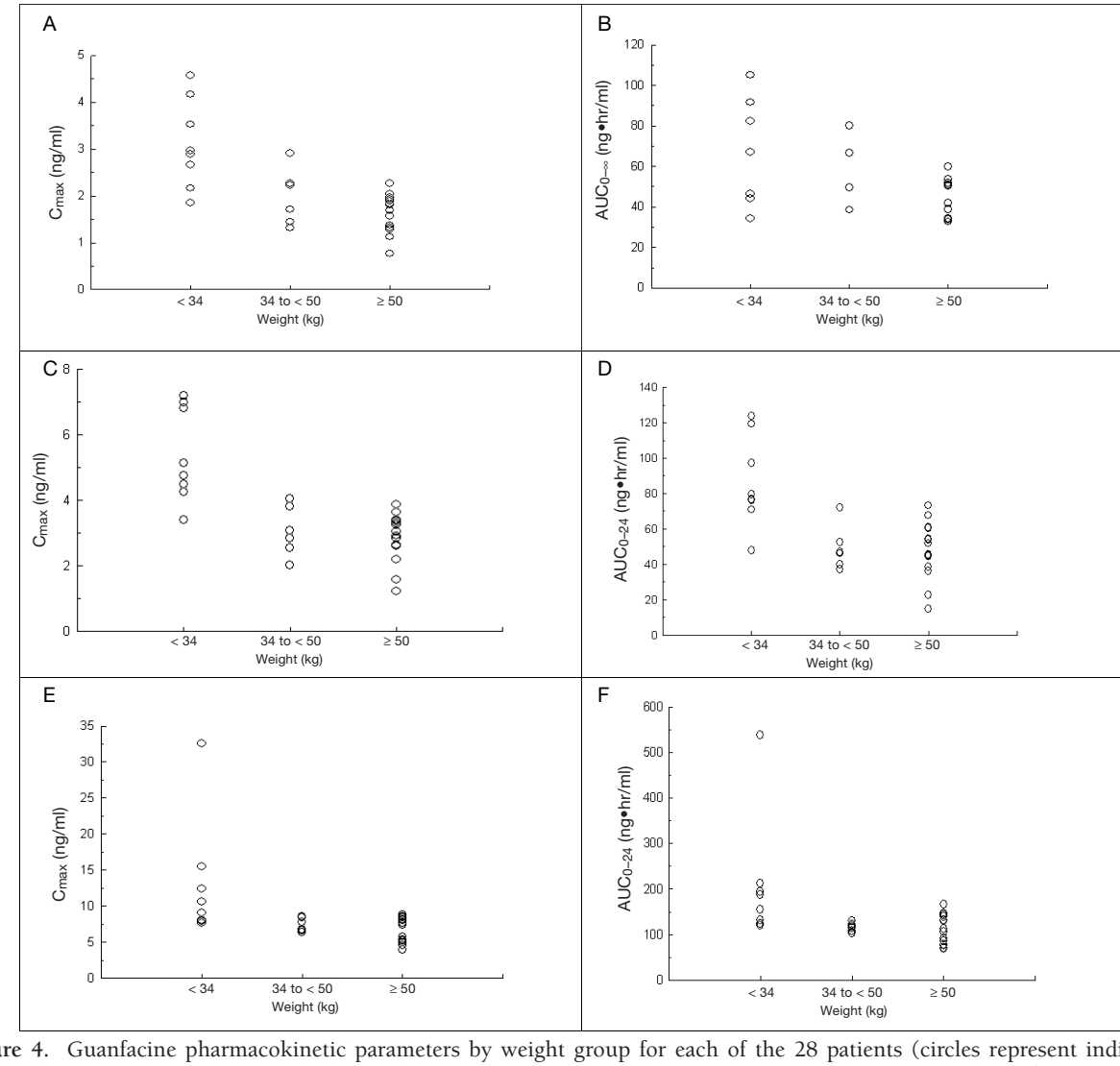

Figure 4. Guanfacine pharmacokinetic parameters by weight group for each of the 28 patients (circles represent individual patients): day-1 maximum concentration (C_{max}; panel A) and area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$; panel B) after a single, 2-mg dose; day-14 C_{max} (panel C) and area under the concentration-time curve from time 0–24 hours (AUC_{0-24}; panel D) after multiple, 2-mg daily doses from days 9–15; and day-28 C_{max} (panel E) and AUC_{0-24} (panel F) after multiple, 4-mg daily doses from days 23–29.

Table 6. Summary of Treatment-Emergent Adverse Events Associated with a Guanfacine Extended-Release Formulation

	2-mg Single Dose (n=28)		2-mg Multiple Dose (n=28)		4-mg Multiple Dose (n=28)		Total (n=28)	
Adverse Events	No. (%) of Subjects with an AE	No. of AEs	No. (%) of Subjects with an AE	No. of AEs	No. (%) of Subjects with an AE	No. of AEs	No. (%) of Subjects with an AE	No. of AEs
Total	3 (11)	4	7 (25)	42	25 (89)	67	27 (96)	113
Possibly related or related to study drug	1 (4)	1	5 (18)	38	23 (82)	59	26 (93)	98
Severe	1 (4)	1	1 (4)	1	5 (18)	5	7 (25)	7
Serious[a]	0	0	0	0	0	0	0	0

AE = adverse event.
[a]Two serious adverse events, appendicitis and peritonitis, were reported in the same subject after the study and were not considered related to the guanfacine extended-release formulation.

$AUC_{0-\infty}$ or AUC_{0-24} values (Figure 4, Table 4). In addition, compared with male subjects, female subjects showed higher mean plasma drug concentrations, C_{max}, and $AUC_{0-\infty}$ or AUC_{0-24} values (Table 5). This result may reflect a difference in body weight between the boys and girls, since girls had body weights that were 9.3% lower among children and 7.8% lower among adolescents.

There were no significant correlations between plasma drug concentrations (all or maximum) and systolic blood pressure, diastolic blood pressure, pulse rate, QTcB, or QTcF.

Safety

No deaths occurred during the study, and no adverse events required study termination. During the follow-up poststudy period, two serious adverse events (appendicitis and peritonitis) occurred in the same subject but were not related to guanfacine extended release.

The frequency and severity of treatment-emergent adverse events are summarized in Table 6. Ninety-three percent of subjects experienced treatment-emergent adverse events that were considered related or possibly related to guanfacine extended release. Most adverse events were considered mild or moderate in severity. Most adverse events considered related or possibly related to treatment occurred after the administration of multiple 2- and 4-mg doses; a higher frequency was associated with the 4-mg dose.

The most common treatment-emergent adverse events possibly or probably related to guanfacine extended release (≥ 5% of subjects) were somnolence (89.3%), insomnia (14.3%), headache (7.1%), blurred vision (7.1%), and altered mood (7.1%). The number of somnolence adverse events was highest on the first day after an increase in dose, generally decreasing on subsequent days (Table 7). Moreover, compared with the occurrence of somnolence on outpatient days, the rate was higher on days in which subjects were confined to the clinic for 24-hour pharmacokinetic sampling. This procedure required subjects to awaken at 5:00 A.M. for intravenous catheteri-zation and hindered return to sleep until as late as 1:00 A.M. the following day.

Guanfacine extended release was associated with no clinically significant changes in ECGs, vital signs, physical examinations, or hematology, clinical chemistry, or urinalysis laboratory values. The absence of clinically significant changes was maintained for all dosing regimens (2-mg single, 2-mg multiple, and 4-mg multiple doses) and all phases of the study.

Discussion

In this open-label, dose-escalation study designed to assess the pharmacokinetics of guanfacine extended-release formulation in children and adolescents with ADHD, guanfacine extended release demonstrated linear pharmacokinetics in doses ranging from 2–4 mg/day in both groups. After a single 2-mg dose, T_{max} was approximately 5 hours for both children and adolescents, half-life was higher in adolescents than in children (17.9 hrs vs 14.4 hrs), but all other parameters were higher in the pediatric group versus the adolescent group. At the same time, and for multiple 2- and 4-mg doses of guanfacine extended release, concentration-related pharmacokinetic parameters were higher in children than in adolescents and higher in

Table 7. Frequency of Somnolence Adverse Events by Study Day

Day	Activity	Dose (mg)	No. (%) of Somnolence Adverse Events (n=86)
1	Confinement	2	0 (0.0)
2		NA	1 (1.2)
3		NA	0 (0.0)
4		NA	0 (0.0)
5		NA	0 (0.0)
6		NA	0 (0.0)
7		NA	0 (0.0)
8		NA	0 (0.0)
9	Dose increase	2	12 (14.0)
10		2	10 (11.6)
11		2	3 (3.5)
12		2	1 (1.2)
13		2	1 (1.2)
14	Confinement	2	7 (8.1)
15		2	1 (1.2)
16	Dose increase	3	11 (12.8)
17		3	0 (0.0)
18		3	1 (1.2)
19		3	0 (0.0)
20		3	0 (0.0)
21		3	0 (0.0)
22		3	0 (0.0)
23	Dose increase	4	17 (19.8)
24		4	1 (1.2)
25		4	0 (0.0)
26		4	2 (2.3)
27		4	2 (2.3)
28	Confinement	4	14 (16.3)
29		4	2 (2.3)
30	Begin downward titration	3	0 (0.0)
31		3	0 (0.0)
32		3	0 (0.0)
33		2	0 (0.0)
34		2	0 (0.0)
35		2	0 (0.0)
36	Discontinuation	NA	0 (0.0)
37		NA	0 (0.0)

NA = not applicable.

girls than in boys. The higher concentration-related parameters in children versus adolescent subjects and in female versus male subjects were probably the result of lower body weight. Girls had approximately 10% lower body weights than boys in both the children and adolescent groups. A subgroup analysis of concentration-related parameters by body weight showed that, as weight increased, the parameters decreased. For C_{max}, this trend was definite; for $AUC_{0-\infty}$ or AUC_{0-24}, it was apparent but less pronounced.

Guanfacine extended release was well tolerated in the study, with most adverse events reported as mild to moderate in severity. No deaths occurred during the study, and no adverse event required early termination from the study.

The most frequent adverse event was somnolence, which generally occurred after an increase in dose. Somnolence may have been exacerbated by the subjects' confinement to the clinic for the 24-hour pharmacokinetic sampling on days 1, 14, and 28. During these days, the sampling procedure disrupted the subjects' sleep patterns; to ensure appropriate samples, the subjects were required to be awake for sampling as early as 5:00 A.M. and as late as 1:00 A.M. Moreover, between samples, the clinic provided the subjects with limited stimulation. Thus, the much lower frequency of somnolence on outpatient days supports the hypothesis that the sleep interruption and limited stimulation contributed to the somnolence (Table 7).

At no time during the study did any of the dosing regimens (2-mg single, 2-mg multiple, and 4-mg multiple doses) produce clinically significant changes in ECG parameters, physical findings, vital signs, or laboratory results (hematology, clinical chemistry, and urinalysis). No vital sign assessment showed any marked changes from baseline or any mean postdose measurement outside normal limits.

Conclusion

Guanfacine extended-release formulation demonstrates linear pharmacokinetics when administered in single, oral, daily doses of 2–4 mg to children and adolescents with ADHD. Compared with adolescents, children showed higher plasma drug concentrations and concentration-related pharmacokinetic parameters. In the younger age group, plasma concentrations and concentration-related pharmacokinetic parameters were higher in girls than in boys. These differences were probably the result of the heavier body weight in adolescents compared with children and in boys compared with girls (regardless of age group). In all groups in this study, guanfacine extended release was safe and well tolerated.

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