Pharmacokinetics, Tolerability, and Clinical Effectiveness of Quetiapine Fumarate: An Open-Label Trial in Adolescents With Psychotic Disorders

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Background: This is the first investigation of the pharmacokinetics, tolerability, and efficacy of quetiapine fumarate in adolescents with chronic or intermittent psychotic disorders.

Method: Ten patients with DSM-IV chronic or intermittent psychotic disorders (ages 12.3 through 15.9 years) participated in an open-label, rising-dose trial and received oral doses of quetiapine twice daily (b.i.d.), starting at 25 mg b.i.d. and reaching 400 mg b.i.d. by day 20. The trial ended on day 23. Key assessments were pharmacokinetic analysis of plasma quetiapine concentrations and neurologic, safety, and efficacy evaluations.

Results: No statistically significant differences were observed between 100–mg b.i.d. and 400–mg b.i.d. quetiapine regimens for total body clearance, dose-normalized area under the plasma concentration–time curve, or dose-normalized premorning– or postmorning–dose trough plasma values obtained under steady-state conditions after multiple-dose regimens. No unexpected side effects occurred with quetiapine therapy, and no statistically significant changes from baseline were observed for the UKU Side Effect Rating Scale items that were rated. No serious adverse events or clinically important changes in hematology or clinical chemistry variables were reported. The most common adverse events were postural tachycardia and insomnia. Extrapyramidal side effects improved, as evidenced by significant ($p < .05$) decreases from baseline to endpoint in the mean Simpson-Angus Scale total scores and Barnes Akathisia Scale scores. Quetiapine improved positive and negative symptoms, as shown by significant ($p < .05$) decreases from baseline to endpoint in the mean Brief Psychiatric Rating Scale total score, the Clinical Global Impressions-Severity of Illness scale, and the Modified Scale for the Assessment of Negative Symptoms summary score.

Conclusion: Quetiapine pharmacokinetics were dose proportional in adolescents and were similar to those previously reported for adults. Quetiapine was well tolerated and effective in the small number of adolescents studied.

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Approximately 10% to 30% of patients with schizophrenia develop psychosis before they are 18 years old.[1–3] Children and adolescents who are diagnosed with schizophrenia, mood disorders, or other psychotic disorders are commonly treated with antipsychotic agents. Although the safety and effectiveness of standard and atypical antipsychotic agents have been well studied in adult populations, relatively few clinical trials have evaluated the therapeutic and adverse effects of these agents in children or adolescents with psychotic disorders. The clinical evaluation of pharmacotherapies used to treat these young patients is crucial, especially considering that the problems associated with standard antipsychotic agents—lack of response, extrapyramidal side effects (EPS), tardive dyskinesia, and treatment-refractory symptoms (particularly negative symptoms)—can be more frequent and severe in children and adolescents.[4–8]

Because of these problems, newer atypical agents may be a more appropriate choice for the treatment of adolescent patients. Studies in adults have shown that some atypical antipsychotics are more effective than standard agents against secondary negative symptoms, have a lower incidence of EPS, and produce significant improvements in some refractory patients.[9–12] A few small studies

with the atypical antipsychotics clozapine,[13–16] risperidone,[17] and olanzapine[18] have provided preliminary evidence of efficacy in adolescent patients with treatment-refractory, childhood-onset schizophrenia. In the only controlled trial with one of these atypical agents, clozapine was superior to haloperidol in treatment-refractory adolescent patients, but 44% of patients discontinued treatment because of seizures, hematologic abnormalities, or nonresponse.[6] Results of an open-label study with risperidone in 16 adolescent patients demonstrated its effectiveness for positive and negative symptoms.[17] However, a 6-mg dose of risperidone has been associated with causing significant EPS in adolescent patients.[19] In an open-label trial of 6 adolescent patients, olanzapine improved positive and negative symptoms relative to baseline.[18]

We investigated the multiple-dose pharmacokinetics, tolerability, and efficacy of the new atypical antipsychotic quetiapine fumarate in adolescent patients with selected psychotic disorders. Quetiapine, a novel dibenzothiazepine derivative, is indicated for the treatment of psychotic disorders, including schizophrenia. Quetiapine binds to a wide variety of neurotransmitter sites, including dopamine-1 (D_1) and D_2 and serotonin-2A ($5\text{-}HT_{2A}$) and $5\text{-}HT_{1A}$, but has a greater affinity for the $5\text{-}HT_2$ receptor site.[20] This combination of receptor antagonism is thought to contribute to the antipsychotic properties and low EPS liability of quetiapine.

In clinical trials with quetiapine, consistent therapeutic benefits were observed for adult patients who had both positive and negative symptoms of schizophrenia.[21–24] In comparative clinical trials, quetiapine was as effective as standard antipsychotic agents, such as chlorpromazine and haloperidol.[11,23] In clinical trials, quetiapine has been well tolerated by patients, with no observations of hematologic abnormalities or corrected QT interval (QTc) prolongation.[21,23,24] Clinical trials have also shown that, across the dose range, quetiapine was not associated with treatment-emergent EPS or concomitant use of anticholinergic medications for treating EPS.[22–24] Unlike standard antipsychotic agents, quetiapine did not elevate plasma prolactin levels.[22–24]

Quetiapine is extensively metabolized in humans, with less than 1% of the administered dose excreted unchanged in the urine and feces.[25] Quetiapine is metabolized primarily by cytochrome P450 3A4 (to its major but inactive sulfoxide metabolite) and to a much lesser extent by cytochrome P450 2D6.[26] In adult subjects, and within the proposed clinical dose range, the multiple-dose pharmacokinetics of quetiapine are linear, and the mean terminal half-life is about 6 hours.[25] Quetiapine is rapidly absorbed after oral administration, reaching peak plasma concentrations in about 1.5 hours.[25] Its bioavailability is not affected by the administration of food.[25]

In this article, we report results from the first trial to investigate the multiple-dose pharmacokinetics, tolerability, and efficacy of the new atypical antipsychotic quetiapine fumarate in adolescent patients with selected psychotic disorders.

MATERIALS AND METHODS

Patient Population and Study Design

A total of 10 female and male adolescent patients aged 12.3 through 15.9 years and weighing between 48.2 and 95.5 kg were enrolled in this open-label, rising- and multiple-dose, tolerability, and pharmacokinetic trial. To be eligible for this study, patients had to have a chronic or intermittent psychosis with a documented clinical diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, major depressive disorder, or bipolar disorder (criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[27]).

A history of tolerability to antipsychotic treatment was a criterion for participation; however, use of depot formulation antipsychotics within 1 dosing interval before trial entry was not permitted, nor was current treatment with clozapine. Similarly, the use of drugs known to alter or induce metabolic enzymes, including barbiturates, carbamazepine, thioridazine, or phenytoin, was not permitted within 6 weeks of trial entry. Patients who took lithium for underlying psychiatric disorders were on a stable dose for at least 1 month before participating in the trial.

Primary exclusion criteria included patients with alcohol or psychoactive substance dependence not in full remission, a positive test for drug abuse or pregnancy, and any clinically significant medical conditions that could affect required evaluations or increase the risk of adverse effects with treatment. Each patient's parent or legal guardian and the patient, when possible, provided written informed consent before he or she entered a pretrial screening period, during which baseline physical and psychiatric assessments were made.

Trial Protocol

Patients with chronic or intermittent psychotic disorders who enrolled in the trial were divided into 2 age groups (Group A, 12 through 14 years old; Group B, 15 through 17 years old) to distinguish any pharmacokinetic differences based on age. They resided at the Adolescent Medical Psychiatric Unit or the Clinical Research Center at Children's Hospital Medical Center in Cincinnati, Ohio. The trial was approved by the Institutional Review Board of Children's Hospital Medical Center in Cincinnati, Ohio.

Ongoing treatment with antipsychotics other than quetiapine was discontinued on day 1, before the trial medications began. Patients received oral doses of quetiapine twice daily (b.i.d., at 7:00 a.m. and 7:00 p.m.), beginning with 25 mg b.i.d. on day 3 and continuing with

fixed, stepwise increases, reaching a maximum of 400 mg b.i.d. on day 21. A final dose of 400 mg was given in the morning of day 23 (Table 1). Patients who were unable to tolerate the titration schedule were given up to 6 extra days to reach the maximum dose by adding 2 extra days after days 4, 6, 10, 13, 16, or 19.

Patients were permitted to take chloral hydrate (500–1000 mg/dose; maximum = 2000 mg/day) for agitation or insomnia, benztropine mesylate (1–4 mg orally; 1–2 mg parenterally) for EPS, lithium when part of a stable regimen at trial entry, and acetaminophen (without caffeine) for analgesia.

Blood Sampling

Blood samples to determine plasma quetiapine concentration were collected in heparinized Vacutainer tubes (Becton Dickinson, Franklin Lakes, N.J.) at the following times on days 11 and 23: before the morning dose of quetiapine; after the morning dose at 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, and 12 hours; and on day 23 only after the morning dose at 16, 20, 24, 36, and 48 hours (Table 1). Additionally, blood samples were collected before the first dose of quetiapine on day 3 to determine an assay baseline and just before the morning dose on days 10 and 22 to determine the minimum plasma concentration at the end of the dosing interval (C^{ss}_{min}) for analysis of steady-state conditions (Table 1).

Blood samples were inverted immediately to mix the blood and centrifuged within 15 to 30 minutes after collection. After centrifugation, the plasma was separated, transferred to polypropylene tubes, and stored at –20°C until assayed.

Analytical Methods

Plasma concentrations of quetiapine were determined by a validated procedure involving extraction of quetiapine from alkalinized plasma with ethyl acetate and detection by high-performance liquid chromatography with atmospheric pressure chemical ionization and tandem mass spectrometry. The quetiapine assay had a quantitation range of 2.5 to 500 ng/mL, with an applicable range to 5000 ng/mL by sample dilution with plasma. The method was specific against known metabolites of quetiapine, common analgesics, lorazepam, flurazepam, diazepam, haloperidol, chlorpromazine, benztropine, chlordiazepoxide, chloral hydrate, fluoxetine, imipramine, thioridazine, risperidone, and procyclidine.

Plasma concentration–versus-time data over a 12-hour dosing interval were used to determine the following: maximum observed plasma concentration during the dosing interval (C^{ss}_{max}), time to C^{ss}_{max} (T_{max}), C^{ss}_{min}, area under the plasma concentration–time curve during a 12-hour interval (AUC^{ss}_{τ}), terminal half-life ($t_{1/2}$), oral clearance (CL/f), and apparent oral volume of distribution (V_z/f).

Table 1. Schedule for Quetiapine Administration and Blood Sample Collection[a]

	Quetiapine Dose, mg		
Trial Day	Daily (total)	Morning (7:00 a.m.)	Evening (7:00 p.m.)
3, 4	50	25	25
5	75	25	50
6, 7	100	50	50
8	150	50	100
9, 10[b]	200	100	100
11[b,c]	250	100	150
12, 13	300	150	150
14	350	150	200
15, 16	400	200	200
17	500	200	300
18, 19	600	300	300
20	700	300	400
21, 22[b]	800	400	400
23[b,d]	400	400	NA

[a]The quetiapine titration schedule could be adjusted by adding 2 extra days after days 4, 6, 10, 13, 16, or 19 (up to a total of 6 extra days).
Abbreviation: NA = not applicable.
[b]Blood samples collected for quetiapine C^{ss}_{min} determination before morning dose.
[c]Blood samples collected for quetiapine assay before and up to 12 hours after morning dose.
[d]Blood samples collected for quetiapine assay up to 48 hours after morning dose.

Safety Assessments

Safety and tolerability were evaluated from adverse event reports, subjective reports of symptomatology, and results of physical and electrocardiographic examinations, hematology and clinical laboratory tests, vital signs measurements, and weight measurement.

The UKU Side Effect Rating Scale[28] was used to evaluate the relative tolerability of quetiapine. Three selected items (asthenia, lassitude, or increased fatigability; sleepiness or sedation; and orthostatic dizziness) were evaluated in the morning of days 2 and 25 and approximately 2 hours after each morning dose of quetiapine on days 3 through 23. The severity of each side effect was rated on a scale from 0 (none) to 3 (severe) or 9 (not rated).

Neurologic status was evaluated using the Simpson-Angus Scale,[29] the Abnormal Involuntary Movement Scale (AIMS),[30] and the Barnes Akathisia Scale (BAS)[31] on the morning of day 2 and approximately 2 hours after the morning dose of quetiapine on days 8, 14, and 20. The Simpson-Angus Scale consists of 10 items (including an akathisia assessment) that are scored on a scale of 1 (normal or minimal) to 5 (severe) or 9 (not rated). The BAS consists of an objective assessment of akathisia, 2 subjective assessments (patient's awareness of restlessness and distress related to restlessness), and a global clinical assessment of akathisia. The AIMS includes 10 items that rate abnormal involuntary movements on a scale from 0 (none) to 4 (severe).

Psychiatric Assessments

Psychiatric assessments were completed in the morning of day 2 and approximately 2 hours after the morning dose

on days 8, 14, and 20 using the 18-item Brief Psychiatric Rating Scale (BPRS; 0 to 6 scoring),[32] the Clinical Global Impressions-Severity of Illness scale (CGI-S) and Global Improvement scale (CGI-I); 0 to 7 scoring for both),[33] and the Modified Scale for the Assessment of Negative Symptoms (SANS).[34] The SANS consists of 5 subscales (affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, and attention) with a total of 24 items, including a global rating for each subscale. The 5 subscales and global ratings are scored on a scale from 1 (normal or not at all) to 5 (severe) or 9 (not rated).

Pharmacokinetic and Statistical Methods

The power calculation was based on data from previous pharmacokinetic trials and an assumption of log normally distributed AUC_{τ}^{ss} data. From that, a sample size of 10 patients was considered sufficient to detect a linear relationship between dose and C_{min}^{ss} values with an 80% power and a significance level of .10.

Patients evaluable for the pharmacokinetic analyses were those who met the trial inclusion criteria, completed the trial in compliance with the protocol, and had their first pharmacokinetic profile assessed (received quetiapine through the evening dose on day 11).

Pharmacokinetic data were analyzed using noncompartmental methods. The pharmacokinetic parameters for quetiapine, except $t_{1/2}$, were derived from the concentration-time data collected over a 12-hour dosing interval following the morning doses on days 11 and 23. The value of AUC_{τ}^{ss} for a 12-hour dosing interval was calculated by linear trapezoidal rule; CL/f was calculated as dose/AUC_{τ}^{ss}. Terminal slope and $t_{1/2}$ were estimated from data collected over the 48-hour period following the morning dose of quetiapine on day 23. The value of V_z/f was calculated as $(CL/f)\lambda_z$. Descriptive statistics were used to summarize plasma quetiapine concentrations and pharmacokinetic parameters by trial day.

A 2-way analysis of variance (ANOVA) with model terms for patient and trial day was used to ascertain steady-state conditions, determine dose proportionality, and compare oral clearance between doses. Morning C_{min}^{ss} values obtained on days 10 and 11 (100–mg b.i.d. dose) and days 22 and 23 (400–mg b.i.d. dose) were used to evaluate steady-state conditions; comparisons were made between trial days at each dose level. Dose-normalized values for AUC_{τ}^{ss}, C_{max}^{ss}, and C_{min}^{ss} were used to assess dose proportionality.

Baseline was defined as day 2 for all safety (including UKU data), neurologic, and psychiatric assessments and day 3 for clinical chemistry and hematology tests. All patients who received at least 1 dose of quetiapine were included in safety assessments.

Adverse events were categorized using an in-house dictionary of terms based on the U.S. Food and Drug Administration Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). Individual adverse events were listed and tabulated by body system.

Descriptive statistics, including mean changes from baseline, were used to summarize data from vital signs, weight measurements, and electrocardiograms (ECGs). Hematology and clinical chemistry test results (including thyroid function tests and plasma prolactin concentrations) were examined in terms of trial-day means, mean changes from baseline, individual values outside the appropriate reference range, and adverse events. A 2-way ANOVA with model terms for patient and trial day was used to evaluate changes from baseline in thyroid function test results and plasma prolactin concentrations.

Descriptive statistics were used to summarize UKU data by trial day. The proportion of patients with increases or decreases from baseline in the severity of individual UKU symptoms was determined. An increase from baseline of at least 1 score unit was considered an increase in symptom severity. Likewise, a decrease from baseline of at least 1 score unit was considered a decrease in symptom severity. The mean score test, a normal-approximation test of paired differences with a multinomial distribution, was used to evaluate changes from baseline for individual items at a significance level of .05.

Neurologic assessment scores and changes from baseline were summarized by trial day with descriptive statistics. The Simpson-Angus Scale total score was calculated as the sum of scores for all items except those that were missing or not ratable. The AIMS total score was calculated as the sum of the scores for the 10 scale items. If 1 score from any visit was missing or not rated for Simpson-Angus Scale and AIMS, the total score was calculated as the sum of the remaining 9 scores multiplied by 1.11 (the ratio of the 10 scale items to the 9 items scored). If more than 1 score for any visit was missing, the total score for the Simpson-Angus Scale and AIMS was considered missing for that visit. On this basis, the total score was considered missing for 1 patient at screening and at visit 2 for both the Simpson-Angus Scale and the AIMS, and the total score was considered missing for 1 other patient at visit 2 for the Simpson-Angus Scale only. Changes from baseline in the Simpson-Angus Scale total score were analyzed by a paired t test. The nonparametric Wilcoxon rank sum test was used to analyze changes from baseline in the AIMS total score and BAS scores (including global clinical assessment of akathisia and objective and subjective measures). Because data from the AIMS total score and BAS scores were not normally distributed, it was determined that the nonparametric Wilcoxon rank sum test was better suited for the analysis of these data.

Psychiatric assessment scores (BPRS total, CGI-S, CGI-I, and SANS summary scores) were summarized by trial day with descriptive statistics. Changes from baseline were calculated for BPRS total, CGI-S, and SANS

Table 2. Demographic Characteristics

Characteristic	Age Group 12–14 y (N = 8)	Age Group 15–17 y (N = 2)	All (N = 10)
Gender, N			
Boys	5	0	5
Girls	3	2	5
Age, y, mean (range)	13.1 (12.3–13.8)	15.9 (15.9)	13.6 (12.3–15.9)
Weight, kg, mean ± SD	66.2 ± 15.6	67.0 ± 9.1	66.4 ± 14.1
Height, cm, mean ± SD	159.2 ± 7.8	164.5 ± 10.6	160.3 ± 8.0
Race, N (%)			
White	5 (62)	1 (50)	6 (60)
Black	3 (38)	1 (50)	4 (40)

summary scores. Because the CGI-I assessed change from screening, no change from baseline was calculated. Psychiatric assessment scores, including mean changes from baseline, were summarized by trial day with descriptive statistics. The BPRS total score was calculated as the sum of scores for all scale items. If 2 or fewer scores for any visit were missing, the total score was calculated as the sum of the remaining scores multiplied by the ratio of the number of scale items (18) to the number of items scored. If more than 2 scores for any visit were missing, the total score was considered missing. On this basis, the total score for 1 patient was considered missing for the BPRS at the screening visit. The summary score for the SANS was calculated as the sum of the global ratings for the 5 SANS subscales. The sexual interest item of the anhedonia subscale was not rated for any patient during the trial. It was held by the clinical investigators that the prepubertal and postpubertal mix of patients and the adult nature of this item impaired its validity for this mixed group. A paired t test was used to analyze changes from baseline in the BPRS total and SANS summary scores; the nonparametric Wilcoxon rank sum test evaluated changes from baseline in the CGI-I.

RESULTS

Demography

All patients completed the trial. The mean age of patients enrolled in the trial was 13.6 years (range, 12.3–15.9 years; Table 2). Table 3 presents patient psychiatric histories and a listing of the medications taken by patients 6 weeks before they entered the trial. Seven patients were diagnosed with schizoaffective disorder and 3 were diagnosed with bipolar disorder with psychotic features (see Table 3). Their mean age at first treatment was 11.5 years (range, 8–15 years).

Pharmacokinetics

Quetiapine was rapidly absorbed after oral administration, with T_{max} ranging from 0.5 to 2.0 hours for the 100–mg b.i.d. dose and 1.0 to 3.0 hours for the 400–mg b.i.d. dose (Table 4). No statistically significant difference was observed between the doses for CL/f. Mean concentration–time profiles showed that the plasma quetiapine concentration increased with dose from 100 mg b.i.d. to 400 mg b.i.d. (Figure 1).

The pharmacokinetic profiles for both dose levels were obtained under steady-state conditions, with no statistically significant differences in C_{min} for the 100–mg b.i.d. doses (C_{min} before the morning doses on days 10 and 11 were 38.9 and 35.8 ng/mL, respectively) or the 400–mg b.i.d. doses (C_{min} before the morning doses on days 22 and 23 were 123.4 and 122.4 ng/mL, respectively). No statistically significant difference was observed between 100– and 400–mg b.i.d. doses in dose-normalized AUC_{τ}^{ss} (13.5 vs. 10.2 ng · h/mL, respectively; p = .07) or C_{min}^{ss} at the end of the interval following the morning dose (0.21 vs. 0.19 ng/mL, respectively; p = .39), indicating dose proportionality (see Table 4). Although the difference in dose-normalized C_{max}^{ss} was significant between 100– and 400–mg b.i.d. doses (3.9 vs. 2.5 ng/mL, respectively; p = .03), the range of dose-normalized C_{max}^{ss} values for the 400–mg b.i.d. dose (1.2–3.8 ng/mL) was within the range of values for the 100–mg b.i.d. dose (1.2–6.5 ng/mL).

Table 3. Patient History and Medications Taken by Patients 6 Weeks Before Entering the Trial

Patient	Age (y)	Sex	Diagnosis	Age at First Treatment (y)	Medication
1	13.8	M	Schizoaffective disorder	8	Haloperidol, lithium carbonate, propranolol, pemoline
2	13.6	F	Schizoaffective disorder	12	Risperidone,[a] venlafaxine
3	13.3	F	Schizoaffective disorder	12	Risperidone, sertraline, alprazolam
4	12.3	M	Bipolar disorder w/psychotic features	10	Olanzapine, valproate, dextroamphetamine
5	13.6	F	Schizoaffective disorder	10	Risperidone
6	12.7	M	Schizoaffective disorder	12	Risperidone, sertraline
7	12.7	M	Bipolar disorder w/psychotic features	11	Perphenazine, valproate, paroxetine
8	13.4	M	Bipolar disorder w/psychotic features	12	Risperidone[a]
9	15.9	F	Schizoaffective disorder	15	Risperidone,[a] valproate, sertraline, propranolol
10	15.9	F	Schizoaffective disorder	13	Olanzapine, valproate, sertraline

[a]Medication used more than 6 weeks before the trial.

Safety

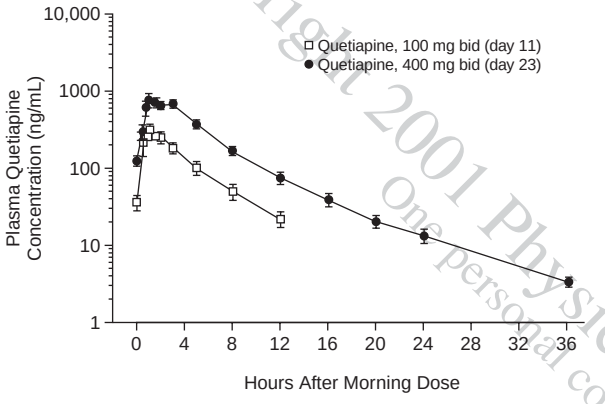
Adverse events. No patients were withdrawn from quetiapine therapy because of adverse events. Adverse events

Table 4. Pharmacokinetic Parameters by Dose[a]

Dose	C^{ss}_{min} (ng/mL)	C^{ss}_{max} (ng/mL)	T_{max} (h), range	$t_{1/2}$ (h)	AUC^{ss}_{τ} (ng·h/mL)	CL/f (L/h)	V_z/f (L)
100 mg bid (day 11)	21.9 ± 4.8	391 ± 59.4	0.5–2.0	NC	1322.6 ± 223.0	95.2 ± 16.0	NC
400 mg bid (day 23)	74.3 ± 13.1	991.9 ± 99.1	1.0–3.0	5.3 ± 0.4	4065.0 ± 340.1	107.0 ± 12.1	792.7 ± 74.2

[a]Values shown as mean ± SEM unless specified otherwise. Abbreviations: AUC^{ss}_{τ} = area under the plasma concentration–time curve during a 12-hour interval, CL/f = oral clearance, C^{ss}_{max} = maximum observed plasma concentration during the dosing interval, C^{ss}_{min} = minimum observed plasma concentration at the end of the dosing interval, NC = not calculated, $t_{1/2}$ = terminal half-life, T_{max} = time to C^{ss}_{max}, V_z/f = apparent oral volume of distribution.

Figure 1. Plasma Quetiapine Concentration (mean ± SEM)–Time Profiles for the 100–mg b.i.d. and 400–mg b.i.d. Doses of Quetiapine



were mild or moderate, with no serious events reported during treatment. The most common adverse events were postural tachycardia (9 patients), initial insomnia (5 patients), and a laboratory finding of decreased total thyroxine (T_4; 4 patients). All events were considered related to treatment, except for 1 case of insomnia. The postural tachycardia seemed to be related to an increase in dosage of quetiapine and started at a total daily quetiapine dose of 150 mg. The initial insomnia seemed to occur at the lower dose range of this study (25–100 mg b.i.d.), and it resolved as the dosage was increased. The incidence of hypothyroidism (defined in this study using the COSTART synonym term of decreased thyroxine) was noted only on day 23 of the trial, when the dose of quetiapine was up to 400 mg b.i.d. In addition to the more common adverse events, infrequent occurrences (1 or 2 patients) were reported of headache, decreased creatinine, eye infection, increased prolactin, agitation, accidental injury, eosinophilia, anemia, leukopenia, and abnormal ECG. No clinically significant sequelae resulted from these events. Since all of these patients continued in an open-label study, it is not possible to comment on whether the adverse events reverted to normal after discontinuation of quetiapine.

Because of the reported incidence of cataracts in animal models exposed to high doses of quetiapine, we are assessing the possible incidence of cataracts in a longer-term open-label follow-up study. So far, no lenticular abnormalities have been found on slit-lamp examinations over a 12-month period.

Tolerability. Most patients tolerated the titration schedule well. One patient required slower titration on days 16 (200 mg b.i.d.) and 19 (300 mg b.i.d.) because of orthostatic dizziness on both days; this subsequently improved. Another patient had a delay in titration from 50 mg b.i.d. to 100 mg b.i.d., due to a preexisting cardiac abnormality that required further investigation, as noted below. One further subject had a technical delay in dosage increase because of difficulty inserting the angiocatheter for the multiple samples required on day 11.

Hematology and clinical laboratory tests. Hematology and clinical laboratory test results revealed no clinically important variations over time. Although free (–2.06 pmol/L, $p = .013$) and total T_4 (–27.67 nmol/L, $p < .001$) concentrations decreased significantly from baseline to day 23, these decreases were not accompanied by a mean increase in thyrotropin (change from baseline = 0.4 mIU/L). The 4 patients showing degrees of hypothyroidism had total T_4 levels of 38.6, 46.3, 48.9, and 52.8 nmol/L, but did not require replacement thyroid treatment. Other patients showed no clinically significant thyroid abnormalities from the normal range of 71 to 160 nmol/L. Plasma prolactin concentrations decreased from baseline to day 23 for girls (–12.6 μg/L) and remained relatively unchanged for boys. No elevations were noted for any liver function test enzymes.

Vital signs and weight. Nine patients had mild or moderate postural tachycardia. The supine pulse rates for these patients ranged from 68 to 96 beats per minute at baseline and from 80 to 92 beats per minute on day 20; standing pulse rates ranged from 72 to 114 beats per minute at baseline and from 100 to 134 beats per minute on day 20.

Six of 10 patients gained weight during the trial, with the mean weight of patients increasing from 66.4 kg at trial entry to 67.9 kg at the time of discharge. Of these 6 patients, weight gain ranged from as little as 0.5 kg to 5.5 kg with a mean weight gain of 1.5 kg.

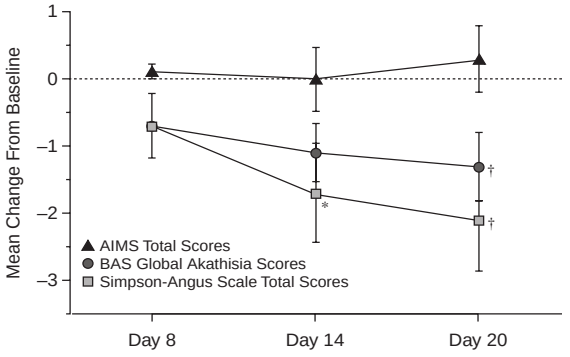
ECG results. Heart rate increased from screening to day 20 of quetiapine therapy (11.4 beats per minute). This increase in heart rate was consistent with the increase in pulse rate observed during vital signs measurements. The mean PR interval, QRS complex, QT interval, and QTc revealed minimal change after quetiapine treatment.

Table 5. Scores (mean ± SEM) at Baseline (day 2) and Day 20 for Neurologic and Psychiatric Assessments[a]

Assessment	Patients (N)	Timepoint Baseline	Timepoint Day 20	p Value[b]
Simpson-Angus Scale total score	10[c]	13.0 ± 0.87	11.2 ± 0.51	.02
BAS				
Global clinical assessment	10	1.4 ± 0.52	0.1 ± 0.10	.02
Objective scale	10	0.6 ± 0.31	0.2 ± 0.13	.30
Subjective scale				
Awareness of restlessness	10	0.9 ± 0.28	0.1 ± 0.10	.02
Distress related to restlessness	10	0.6 ± 0.27	0 ± 0	.03
AIMS total score	10	0.5 ± 0.40	0.8 ± 0.36	.38
BPRS total score	10	39.3 ± 4.98	13.5 ± 3.02	.001
CGI				
Severity of Illness	10	5.2 ± 0.29	3.1 ± 0.35	.001
Global Improvement[d]	10	NA	2.2 ± 0.36	NA
SANS summary score	10	13.6 ± 1.63	8.3 ± 1.01	.0006

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, SANS = Scale for the Assessment of Negative Symptoms.
[b]p Value for change from baseline to day 20.
[c]N = 9 for baseline assessment.
[d]Day 20 result is not compared with baseline (day 2).

Figure 2. Change From Baseline (day 2) Through Day 20 in Neurologic Assessment Scores for Adolescent Patients Treated With Quetiapine



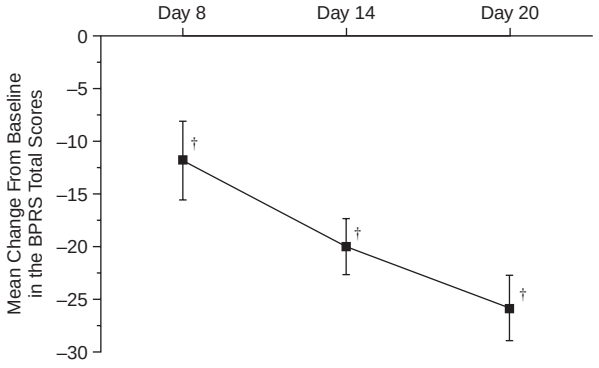
*p = .05.
†p < .05.

No patients had a QTc greater than 0.5 seconds or changes from baseline of 0.06 seconds or more at any time during the trial. One patient had a preexisting ECG abnormality: a first-degree AV block that was determined by the cardiologist to be stable enough for participation in the trial.

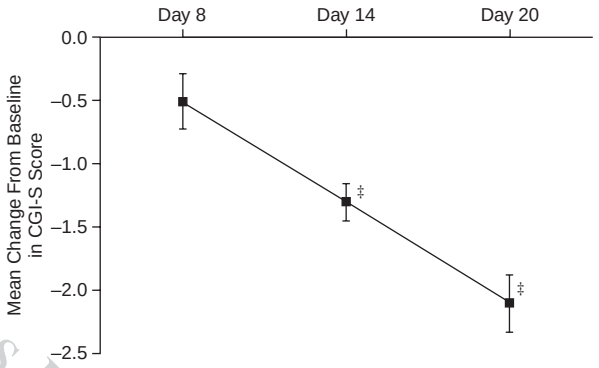
UKU rating. No unexpected side effects occurred during quetiapine therapy. The only side effect rating that worsened in 25% or more of the patients was asthenia/lassitude/fatigue, a known effect of quetiapine. Most patients had little change in their UKU ratings during treatment. No statistically significant mean changes from baseline were observed on any trial day for any of the UKU items rated.

Figure 3. Change From Baseline (day 2) Through Day 20 in (A) BPRS Total Scores and (B) CGI-Severity of Illness (CGI-S) Scores for Adolescent Patients Treated With Quetiapine

A.



B.



†p < .05.
‡p < .01.

Neurologic assessments. Quetiapine therapy did not induce EPS, but rather improved existing EPS over the course of the trial. A significant (p = .02) decrease from baseline to day 20 occurred for the Simpson-Angus Scale total score and BAS global clinical assessment of akathisia score (Table 5, Figure 2). For the BAS, a decrease from baseline to day 20 was also evident for objective and subjective subscales (see Table 5). No patients withdrew from the trial because of EPS or required treatment with benztropine for EPS.

Changes in the AIMS total score were minimal from baseline to day 20 of quetiapine therapy, indicating that patients had little evidence of involuntary movement before or after therapy (see Figure 2).

Psychiatric assessments. Quetiapine improved psychotic symptoms in those with either schizoaffective or bipolar disorders with psychotic features, as shown by a significant (p ≤ .001) decrease from baseline to day 20 in the BPRS total score and CGI-S (Figures 3A and 3B; see

Table 5). A decrease from baseline to day 20 was also observed for the CGI-I score (see Table 5). Negative symptoms improved as demonstrated by a significant ($p = .0006$) decrease from baseline to day 20 in the mean SANS summary score (see Table 5).

DISCUSSION

In this trial of adolescents with selected psychotic disorders, the administration of quetiapine over a dose range of 50 to 800 mg daily led to satisfactory clinical results. The pharmacokinetics of quetiapine were dose proportional, as demonstrated by no statistically significant difference between 100– and 400–mg b.i.d. doses in dose-normalized AUC^{ss}_{τ} or C^{ss}_{min}. A significant ($p < .05$) difference was observed between doses for dose-normalized C^{ss}_{max}; however, the mean and several individual concentration profiles for the 400–mg b.i.d. dose showed significant double peaks around T_{max}. We attribute this finding to the administration of two 200-mg tablets for the 400-mg dose and only one 100-mg tablet for the 100-mg dose. The reduced values and relatively large variability in C^{ss}_{max} values for the 400-mg dose may be caused by differences in the absorption rates of the 2 tablets administered for this dose. This phenomenon is probably related to the uncertainty of complete gastric emptying of both tablets at once to the duodenum.

The pharmacokinetic profile of quetiapine in adolescents was similar to the profile previously observed for adults. For adolescents, $t_{1/2}$ and T_{max} were 5.3 hours (mean) and 0.5 to 3.0 hours (range), respectively. Corresponding values for adults were 6 hours and 1.5 hours, respectively.[25] CL/f values (mean ± SEM) for adolescents after the 100– and 400–mg b.i.d. regimens were 95 ± 16 and 107 ± 12 L/hour, respectively. In a previous trial, a CL/f value of 101 ± 11 L/hour was reported for adult men and women who were given a 300–mg b.i.d. dose of quetiapine.[35] Therefore, from a pharmacokinetic standpoint, no dosage adjustment should be required when treating adolescent patients with quetiapine.

Quetiapine was well tolerated by the adolescents in this trial. No new safety issues arose during therapy, and the side effect profile of quetiapine in adolescents was similar to that of adults.[21–24] Three patients reporting asthenia on the UKU during quetiapine therapy did not report improvement or resolution on the last day of treatment.

The occurrence of postural tachycardia in 9 of 10 patients during this trial may have reflected reflex tachycardia in response to orthostatic hypotension. Patients' heart rates increased during quetiapine therapy. Mean increases in standing pulse were accompanied by small decreases in systolic blood pressure over the course of the trial.

Clinical laboratory test findings were consistent with those observed for adults who were treated with quetiapine. As in adults, small decreases in mean total and free T_4 were observed; however, the decrease in T_4 was not accompanied by a concomitant increase in thyrotropin.[11,22–24] Moreover, all patients were asymptomatic, and no event was associated with clinical hypothyroidism.

Prolactin levels were not adversely affected by quetiapine therapy. The lack of sustained serum prolactin elevations in adolescents corroborates findings from studies in adults.[11,22–24] This characteristic of quetiapine therapy helps distinguish the drug from standard antipsychotic agents and suggests that patients will not experience adverse events associated with prolactin elevations (i.e., amenorrhea, impotence, and galactorrhea).

Neurologic evaluations indicated that quetiapine, unlike standard antipsychotic agents, did not induce EPS. In fact, mean Simpson-Angus Scale and BAS scores decreased over the course of therapy, indicating improved EPS. Also, no patients required treatment or withdrew from the trial because of EPS. Low EPS liability is an important characteristic, especially when choosing an antipsychotic agent for adolescent patients, a population that is particularly prone to EPS. If treatment is not compromised by EPS, compliance with therapy may improve and so may outcomes. Additionally, the lack of treatment-induced EPS in this trial confirms results from other studies in sensitive patient populations, such as elderly patients and patients with Parkinson's disease, and provides further evidence to support the use of quetiapine in these sensitive populations.[36,37]

Clinically, quetiapine improved both positive and negative symptoms in the chronically ill adolescent patients studied. Patients in this trial had significant ($p < .05$) improvements from baseline to endpoint in the BPRS total, CGI-S, and SANS summary scores. These findings extend those of placebo-controlled studies in adults in which quetiapine improved both positive and negative symptoms of schizophrenia.[11,21–23] These preliminary findings in adolescents may also have important clinical implications for adults. Research suggests that early effective pharmacologic intervention can improve long-term outcomes in adults (i.e., progression of schizophrenia, deterioration, and morbidity).[38–40]

This trial was limited by several design factors such as the small number of patients, the open-label nature of the study, inclusion of various diagnostic categories, and patients' previous exposure to a number of antipsychotic medications. However, these preliminary results indicate that quetiapine given to adolescents at doses within the recommended treatment range for adults has a pharmacokinetic and safety profile similar to that for adults. Quetiapine was well tolerated by adolescent patients and was effective in reducing both positive and negative symptoms. Additionally, quetiapine may offer treatment benefits over other therapies in that it does not induce EPS and is not associated with the risk of agranulocytosis or sus-

tained prolactin elevations. The positive findings from this trial justify further investigations of quetiapine in larger, controlled clinical trials in adolescents.

Drug names: alprazolam (Xanax and others), benztropine mesylate (Cogentin and others), carbamazepine (Tegretol and others), chlordiazepoxide (Librium and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), dextroamphetamine (Dexedrine and others), diazepam (Valium and others), fluoxetine (Prozac), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Paxil), pemoline (Cylert), phenytoin (Dilantin and others), procyclidine (Kemadrin), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thioridazine (Mellaril and others), venlafaxine (Effexor).

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