Drug Substance(s)	quetiapine fumarate	**SYNOPSIS**	(For national authority use only)
Study Code	D1441C00028		
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A Study to Characterize the Steady-State Pharmacokinetics, Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) in Children and Adolescents with Selected Psychotic Disorders

Investigator

Study centers

Study centers that entered subjects were located in California, Nevada and Arkansas.

Study dates		**Phase of development**
First subject enrolled	23 March 2004	Clinical pharmacology (I)
Last subject completed	3 September 2004	

Objectives

Primary Objective:

To characterize the steady-state pharmacokinetics (PK) of quetiapine fumarate (SEROQUEL™, quetiapine) administered as quetiapine tablets in children and adolescents 10 to 17 years of age.

Secondary objectives:

1. To monitor the tolerability and safety of titrating doses of quetiapine
2. To determine the dose-proportionality for quetiapine
3. Compare the AUC and C_{max} between the subjects in this trial and D1441C00130
4. To characterize the PK of 3 metabolites: quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine

Study design

This was a multicenter, open-label, inpatient, steady-state, PK, safety and tolerability study in children and adolescents with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease. Quetiapine was administered in divided doses for 13 days, with titration up to a total daily dose of 800 mg over 11 days. Plasma and urine concentrations of quetiapine and its metabolites were measured after the morning doses were administered on Day 7 (200-mg dose) and Day 13 (400-mg dose). Safety was assessed by recording adverse events (AEs) and collecting vital signs measurements, electrocardiographic (ECG) data and clinical laboratory tests.

Target subject population and sample size

The target subject population comprised children and adolescents ages 10 to 17 years with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease. The target sample size was a minimum of 24 subjects evaluable for PK analysis (ie, subjects who met the selection criteria and completed the study in compliance with the protocol), with up to as many as 30 subjects exposed to study drug.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The study used intact quetiapine 25-mg tablets (formulation number F12804; batch number 2000058452; lot number 7527F) and 100-mg tablets (formulation number F12689; batch number 2000058452; lot number 7511H) that were administered orally, every 12 hours. Subjects received ascending total daily doses of quetiapine, administered in equally divided doses twice daily unless noted otherwise, as follows: Day 1 (a single 50-mg dose in the evening), Day 2 (100 mg), Day 3 (200 mg), Day 4 (300 mg), Days 5 to 7 (400 mg), Day 8 (500 mg), Day 9 (600 mg), Day 10 (700 mg), Days 11 and 12 (800 mg), and Day 13 (a single 400-mg dose in the morning).

Duration of treatment

Subjects were to receive study medication for 13 days.

Variables

- **Pharmacokinetic**

  Blood samples: AUC_{ss}, $C_{ss,max}$, $C_{ss,min}$, $t_{1/2}$, t_{max}, CL/F, Fu, $Ael_{(m)}$, CL_R, and λ_z for quetiapine and AUC_{ss}, $C_{ss,max}$, $C_{ss,min}$, $t_{1/2}$, t_{max}, Fu, $Ael_{(m)}$, CL_R, and λ_z for 3 metabolites (quetiapine sulfoxide, 7-hydroxy quetiapine, and N-desalkyl quetiapine). AUC_{ss} and $C_{ss,max}$ following the 200-mg and 400-mg morning doses on Days 7 and 13 were the primary variables.

  Urine samples: Fu and $Ael_{(m)}$ for quetiapine 4 metabolites (quetiapine sulfoxide, 7-hydroxy quetiapine, N-desalkyl quetiapine and 7-hydroxy N-desalkyl quetiapine).

- **Safety**

  Incidence and severity of AEs, serious AEs and discontinuation due to AEs, clinical laboratory tests (chemistry, hematology and urinalysis) vital sign measurements, and 12-lead ECGs.

Statistical methods

Plasma concentrations and PK parameters for quetiapine and its metabolites were summarized descriptively for each dose for all subjects and by age group (10-12 years and 13-17 years).

To assess the dose-proportionality of quetiapine, log-transformed AUC_{ss} and $C_{ss,max}$ for the 400-mg morning dose were compared to the log-transformed AUC_{ss} and $C_{ss,max}$ for the 200-mg morning dose, respectively, using analysis of variance (ANOVA) methods.

Comparisons of exposure in children/adolescents with that in adults (from Study D1441C00130) used the following models: log-transformed, dose-normalized AUC_{ss} and $C_{ss,max}$ were analyzed separately using ANOVA with a term for age group (ie, 10- to 17-year-old subjects or adult subjects). Least squares means and 90% confidence intervals for the ratios of interest (ie, AUC_{ss} for 10- to 17-year-olds:AUC_{ss} for adults and $C_{ss,max}$ for 10- to 17-year-olds:$C_{ss,max}$ for adults) were calculated. If the 90% confidence intervals for both AUC_{ss} and $C_{ss,max}$ were completely contained within the interval 0.71 to 1.41, it was concluded that there was no difference in exposure between adults and 10- to 17-year-old subjects. These comparisons were performed for quetiapine and for the 3 metabolites.

Descriptive statistics were used to summarize clinical laboratory test results, vital signs, and ECG data. Adverse events were classified using MedDRA, and were grouped by system organ class and preferred term. The incidence of AEs occurring before, during and after treatment was summarized for all subjects and for subjects by age group.

Subject population

Twenty-eight subjects were enrolled in this study. Twenty-seven of the 28 subjects received the study medication; 1 subject was withdrawn from the study after enrollment but prior to receiving study medication. As a result, 27 subjects were included in the safety population. Three additional subjects withdrew from the study prior to completion; therefore, 24 subjects were evaluable for PK analyses. Three subjects in the 10- to 12-year age group were unable to tolerate daily doses above 600 mg and remained on 600 mg per day from Day 11 onward, as allowed by the protocol.

Of the 27 subjects in the safety population, 13 were in the 10- to 12-year age range, and 14 were in the 13- to 17-year age range. The median age of subjects in the safety population was 13 years. In the 13- to 17-year-old age group, 10 of the 14 subjects were 13 or 14 years old. Approximately one-half of the subjects in each age group were male. Approximately one-half of all subjects were Black; the proportion of Blacks was slightly higher in the 13- to 17-year-old age group. All but 1 of the subjects had a diagnosis of bipolar I disorder; 1 subject in the 10- to 12-year-old age group had a diagnosis of schizoaffective disorder.

Summary of pharmacokinetic results

Descriptive statistics for selected quetiapine PK parameters on Day 7 (200 mg) and Day 13 (400 mg) are summarized in Table S1.

Quetiapine was rapidly absorbed with a $C_{ss,max}$ at 1.5 hours after dosing, and had a $t_{1/2}$ of approximately 6 hours. Two of the metabolites, quetiapine sulfoxide and 7-hydroxy quetiapine, had estimates of $t_{1/2}$ similar to quetiapine and can be considered formation-rate limited metabolites; ie, they cannot be eliminated faster than they are being formed. The N-desalkyl quetiapine metabolite had a longer $t_{1/2}$ than quetiapine and is an elimination rate-limited metabolite; ie, it is eliminated more slowly than it is formed. Preliminary estimates of the $t_{1/2}$ for N-desalkyl quetiapine ranged from 7.4 to 20.5 hours. In terms of in vivo exposure, the rank order of exposure with respect to both AUC_{ss} and $C_{ss,max}$ was:

quetiapine sulfoxide>quetiapine>N-desalkyl quetiapine>7-hydroxy quetiapine.

Urinary excretion of quetiapine and its metabolites appeared to be minor. Dose-proportionality of the 200-mg and 400-mg morning doses was demonstrated for both AUC_{ss} and $C_{ss,max}$ for quetiapine and for all 3 metabolites.

Quetiapine AUC_{ss} and $C_{ss,max}$ appeared to be higher in 10- to 12-year-old subjects than in 13- to 17-year-old subjects. Similar trends were observed for the quetiapine sulfoxide and N-desalkyl quetiapine metabolites. However, the high degree of inter-subject variability suggested that these apparent age-related differences in exposure may not be clinically meaningful. There was no apparent association between CL/F and age, weight or BMI.

Table S1 Selected pharmacokinetic parameters for quetiapine in subjects who received the 400-mg morning dose

		Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
PK parameter	Statistic	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric Mean	2560.0	5145.0	1651.4	3784.8	1992.8	4317.1
	CV (%)	56.8	29.1	64.5	46.6	65.0	42.4
$C_{ss,max}$ (ng/mL)	Geometric Mean	707.0	1426.3	414.3	924.7	520.9	1113.4
	CV (%)	37.5	33.9	69.4	51.6	63.9	49.8
t_{max} (hr)	Median	1.08	1.50	1.57	1.50	1.50	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
$t_{1/2}$ (hr)	Mean	3.17	5.52	2.77[b]	5.52[b]	2.96[c]	5.52[c]
	SD	0.99	1.38	0.56	0.77	0.80	1.07

[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] Excludes 2 of 12 subjects for whom $t_{1/2}$ could not be calculated.
[c] Excludes 2 of 21 subjects for whom $t_{1/2}$ could not be calculated.
AUC_{ss} area under the curve at steady-state. $C_{ss,max}$ the maximum plasma concentration at steady-state. $t_{1/2}$ terminal elimination half-life.

A comparison of the pharmacokinetic data from this study and data from a study using the same doses in adults (Study D1441C00130) showed no significant differences in dose-normalized exposure (AUC_{ss} and $C_{ss,max}$) between adults and children/adolescents for either quetiapine or 7-hydroxy quetiapine for the same administered dose. However, these analyses did show statistically significant age-related differences in the quetiapine sulfoxide and N-desalkyl quetiapine metabolites, with estimates of AUC_{ss} that were 27% and 45% higher, respectively, in children/adolescents than those in adults. Comparisons of weight-adjusted, dose-normalized exposure (ie, exposure divided by [dose/weight]) showed evidence for statistically significant age-related differences in exposure to quetiapine and 7-hydroxy quetiapine, with lower exposures seen in children/adolescents. These comparisons of weight-adjusted, dose-normalized exposure showed no evidence for age-related differences in exposure to the quetiapine sulfoxide or N-desalkyl quetiapine metabolites.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic correlations

Not applicable.

Summary of population pharmacokinetics

Not applicable.

Summary of pharmacogenetics

Not applicable.

Summary of safety results

Quetiapine was well tolerated in this population of children and adolescents. There were no deaths or other serious AEs during study treatment. One subject was inappropriately withdrawn from the study based on an incorrect QTc calculation. There were no other discontinuations due to AEs. There were no obvious differences between the age groups in the types of adverse events that occurred, or in their intensity. The majority of adverse events were rated by the investigators as mild in intensity and resolved prior to study completion. No unexpected AEs were reported. Somnolence was the most frequently occurring AE during study treatment. Most of the cases of somnolence occurred shortly after initiation of study treatment (ie, Day 1 or 2) and resolved prior to study completion. Three subjects in the 10- to 12-year-old age group had their study medication doses restricted to 600 mg/day from Day 11 onward. The AEs that limited dosing in 2 of these 3 subjects were dyskinesia and dizziness. The third subject's dose was restricted due to an incorrectly calculated QTc interval; the correctly calculated interval was 407 ms, and the subject's QTcF never rose above 425 ms.

There were no apparent trends over time in hematology test results. Mean changes from baseline were small and not clinically meaningful, and there were no clinically meaningful individual abnormalities. Mean increases from baseline in ALT were seen in both age groups; however, these increases were not unexpected and were not considered clinically meaningful. No other trends over time in clinical chemistry test results were observed. Sporadic treatment-emergent abnormalities were seen in hematology and clinical chemistry test results for individual subjects, but none were considered clinically significant.

There were no obvious trends over time in blood pressures. Mean heart rates tended to increase over time in both age groups, and increases in standing heart rates were generally larger than increases in supine heart rates. Heart rate increases have been seen with quetiapine treatment in previous trials; therefore, these trends were not unexpected. The most frequently occurring potentially clinically significant abnormalities were elevations in standing diastolic blood pressure and elevations or increases from baseline in standing heart rate. Elevations or increases from baseline in these 2 standing measurements were seen on more than 7 days during the treatment period in approximately one-half of the subjects.

There were no apparent trends over time in QTc intervals. Mean changes in QTc tended to be small decreases (which were not clinically meaningful), rather than increases. There were no clinically significant QTc intervals or changes from baseline in QTc intervals.