Multiple-Dose Pharmacokinetics of Fluvoxamine in Children and Adolescents

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ABSTRACT

Objective: To determine the pharmacokinetics of fluvoxamine in children and adolescents and to compare pharmacokinetic data from adolescents to adults from a previous study. Method: Fluvoxamine was titrated to a target dose of 100 mg b.i.d. in children (6–11 years) and 150 mg b.i.d. in adolescents (12–17 years) with obsessive-compulsive disorder or other disorder requiring fluvoxamine treatment. Serum samples were collected over 12 hours after 12 or more consecutive doses of 25, 50, 100, and 150 mg. Results: Sixteen children (seven females, nine males) and 18 adolescents (nine females, nine males) were included in the pharmacokinetic analyses. Children demonstrated higher mean peak plasma concentration, higher mean area under the plasma concentration-time curve, and lower apparent oral clearance compared with adolescents. Compared with male children, female children had higher mean area under the plasma concentration-time curve, higher mean peak plasma concentration, and more reports of adverse events. However, the area under the plasma concentration-time curve was not directly correlated with frequency or severity of adverse events. Pharmacokinetics were nonlinear over the dose range studied. No pharmacokinetic differences were apparent between adolescents and adults on 150 mg b.i.d. Conclusions: These pharmacokinetic results suggest that children (especially females) have a higher exposure to fluvoxamine than adolescents, whereas adolescents and adults appear to have similar exposure to fluvoxamine. J. Am. Acad. Child Adolesc. Psychiatry, 2004;43(12):1497–1505. Key Words: fluvoxamine, pharmacokinetics, anxiety disorders, pediatric.

Of the six selective serotonin reuptake inhibitors (SSRIs) available in the United States, published studies of three SSRIs demonstrated pharmacokinetic exposure data in children and adolescents: multiple-dose studies of sertraline (Alderman et al., 1998) and fluoxetine (Wilens et al., 2002) and a single-dose study of paroxetine (Findling et al., 1999). When adjusted for weight, children and adolescents had similar exposure to sertraline and fluoxetine; children had less exposure to paroxetine than did adolescents. None of the studies suggested special precautions with the doses studied. A study of adolescents treated with citalopram demonstrated steady-state concentrations of enantiomers and demethylated metabolites but no other aspects of citalopram exposure (Carlsson et al., 2001).

This study was conducted to determine the multiple-dose pharmacokinetic parameters of fluvoxamine in children and adolescents with obsessive-compulsive disorder (OCD) or other conditions that may benefit from fluvoxamine treatment. A secondary objective was to compare the pharmacokinetic data from adolescents treated with fluvoxamine with pharmacokinetic data from adults treated with fluvoxamine in a previous study. Controlled treatment studies have demonstrated...
the safety and efficacy of fluvoxamine for OCD (Riddle et al., 2001), separation anxiety disorder, social phobia, and/or generalized anxiety disorder in children and adolescents (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2001). Differences in pharmacokinetic parameters in adolescents compared with children may explain the discrepancy between treatment response observed in children compared with that of adolescents in the fluvoxamine OCD study (Riddle et al., 2001).

METHOD

The nine principal investigators in this multisite clinical study obtained written approval from respective institutional review boards for the study protocol and amendments, the written informed consent and assent forms, and any other written information provided to subjects and parents/legal guardians.

Study Subjects

Male and female outpatients aged 6 to 17 years were required to have OCD or other psychiatric disorders that could benefit from fluvoxamine treatment, diagnosed by a study psychiatrist using criteria of the DSM-IV (American Psychiatric Association, 1994). Each subject was required to measure in the 5th or higher percentile for height and weight and have no clinically significant abnormalities on physical examination, medical history, laboratory testing of serum and urine, and electrocardiogram (ECG). Subjects were required to be nonsmokers or ex-smokers for the 12 months before screening. All female subjects who had reached menarche were required to have a negative serum pregnancy test at the screening and end of study visits. Subjects were assigned to one of two treatment groups based on age at the baseline visit. The child group included subjects aged 6 to 11 years, and the adolescent group included subjects aged 12 to 17 years.

Exclusion criteria for the study included major drug allergy, previous sensitivity to SSRIs or dextromethorphan, and any acute or clinically significant disease that could possibly interfere with the absorption, distribution, metabolism, or excretion of fluvoxamine. Consumption of caffeinated beverages was limited to no more than five servings of coffee, tea, or cola per day before study entry. No xanthine-containing beverages or alcohol were allowed within 48 hours of the baseline visit or throughout the study. Ingestion of any known inhibitor/inducer of CYP450 or investigational drug within the previous 3 months or injection of depot neuroleptics within the previous 3 months excluded subjects from participation. Ingestion of a monoamine oxidase inhibitor within 14 days before baseline also excluded subjects from participation.

A sample size of 32 children and adolescents was selected to detect 100% difference in area under the plasma concentration-time curve (AUC) between groups with 72% power.

Determining Metabolizer Status

Before fluvoxamine treatment, subjects ingested 10 mg dextromethorphan (6.7 mL of syrup containing 7.5 mg dextromethorphan/5 mL). Urine was then collected overnight (28 hours) for assay of dextromethorphan/dextrorphan ratio, a measure of CYP2D6 metabolic activity.

Pharmacokinetic Sampling

This study used two fluvoxamine dose-titration schedules based on stratification by age. Children received fluvoxamine doses up to 200 mg/day in two divided doses 12 hours apart, based on tolerability. Children received fluvoxamine 50 mg/day (25 mg b.i.d.) for the first week, 75 mg/day (25 mg in the morning and 50 mg in the evening) for the second week, 100 mg/day (50 mg b.i.d.) for the third week, 150 mg/day (75 mg b.i.d.) for the fourth week, and 200 mg/day (100 mg b.i.d.) for the fifth week. Adolescents received fluvoxamine doses up to 300 mg/day in two divided doses, based on tolerability. Adolescents received fluvoxamine 50 mg/day (25 mg b.i.d.) for the first week, 100 mg/day (50 mg b.i.d.) for the second week, 150 mg/day (75 mg b.i.d.) for the third week, 200 mg/day (100 mg b.i.d.) for the fourth week, 250 mg/day (125 mg b.i.d.) for the fifth week, and 300 mg/day (150 mg b.i.d.) for the sixth week. The fluvoxamine dose range and schedule were based on similar dosing regimens used in the above pediatric OCD and anxiety treatment studies (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2001; Riddle et al., 2001). The maximal daily dose used in adolescents was similar to the maximal daily dose used in previous clinical studies of adults.

On days of pharmacokinetic sampling, subjects were given their morning dose of fluvoxamine by the clinical staff, who documented the exact time of fluvoxamine dosing. Serum sampling was conducted before dosing (hour 0) and at hours 2, 4, 6, 8, 10, and 12 after the morning dose. For children, sampling occurred after receipt of 50, 100, and 200 mg/day fluvoxamine maleate. For adolescents, sampling occurred after receipt of 50, 100, 200, and 300 mg/day fluvoxamine maleate. To ensure steady state, each subject received a minimum of 12 consecutive fluvoxamine doses at a fixed dose before 12-hour blood sampling was performed.

Clinical Assessments

Efficacy was not assessed during the study. Safety was monitored by adverse event (AE) assessment, physical examination, vital signs, ECG, and laboratory determinants throughout the study. Treatment emergent signs and symptoms were defined as either AEs present at baseline that worsened in severity or AEs that began after treatment with study medication. The abbreviation AE will be synonymous with treatment emergent signs and symptoms in the remainder of this article. All AEs were coded using the COSTART dictionary. AEs were rated by the investigators as mild (e.g., usually transient and not interfering with the patient’s daily activities), moderate (e.g., introduce a low level of inconvenience or concern to the patient and may interfere with daily activities), severe (e.g., interrupt the patient’s usual daily activity), or serious (e.g., life threatening, results in death, results in persistent disability/in- capacity, requires hospitalization or prolongation of existent hospitalization, other important medical events based on appropriate medical judgment). Causal relationship between fluvoxamine and reported AEs was characterized as unrelated, unlikely related, possibly related, probably related, or unknown according to the study physician’s clinical judgment. Before starting fluvoxamine treatment, subjects participated in medical history, physical examination, Tanner staging (Tanner, 1969), 12-lead ECG, vital sign measurements (seated blood pressure and pulse, height, weight, and oral temperature), clinical laboratory assessment (hematology, chemistry, and urinalysis), serum pregnancy screen, urine drug screen, thyroid panel, and hepatitis B screen. Vital sign assessment, AE inquiry, urinary drug screen, and ECG monitoring occurred at each visit. Physical examination, clinical laboratory de-
terminates, and serum pregnancy tests were repeated at the final visit. Vital signs were recorded 15 to 30 minutes before dosing as well as 4 hours post-dose on inpatient sampling days. Additional vital sign monitoring was obtained as needed.

Pharmacokinetic Analyses

Pharmacokinetic parameters measured by serum sampling included maximal plasma concentrations ($C_{\text{max}}$), time to maximal plasma concentrations ($T_{\text{max}}$), minimal plasma concentrations ($C_{\text{min}}$), $AUC_{0–12}$, and apparent oral clearance (oral clearance adjusted for the fraction of drug absorbed [CL/F]). The key parameters of interest, $C_{\text{max}}$, $AUC_{0–12}$, and CL/F, were normalized for body weight.

Concentrations of dextromethorphan and dextrorphan were determined using a liquid chromatography fluorescence method. Patients with a dextromethorphan/dextrorphan metabolic ratio of $<0.3$ were classified as having an extensive metabolizer phenotype and those with a ratio of $>0.3$ were considered as having a poor metabolizer phenotype for the CYP2D6 isoenzyme. Fluvoxamine concentrations were determined using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method (Solvay Pharmaceuticals, Inc., unpublished, 1999). The lower limit of quantification was 0.5 ng/mL fluvoxamine free base.

Statistical Analyses

Noncompartmental pharmacokinetic parameters were calculated from plasma concentrations of fluvoxamine using WinNONLIN™ (Professional Edition 2.1, Pharsight Corporation, Mountain View, CA). All analyses of pharmacokinetic variables were performed using SAS® Version 6.12. Models were fit using PROC MIXED. Ratios and 90% confidence intervals (CIs) were calculated using the ESTIMATE statement in PROC MIXED. Arithmetic means and SDs were calculated using PROC UNIVARIATE. Least-squares means were calculated using the LSMEANS statement in PROC MIXED. All safety analyses were also performed using SAS Version 6.12. $P$ values $\leq .05$ were considered statistically significant.

Descriptive statistics were determined for the pharmacokinetic parameters. The primary objective was addressed by an analysis of covariance (ANCOVA) on both original and dose-normalized pharmacokinetic parameters in child and adolescent patients. The model included dose, gender, Tanner stage, and age group as fixed effects and body weight as a covariate. The ANCOVA model involved pairwise ratios (dose in milligrams; e.g., 50/25, 100/25, 150/25,100/50, 150/50, 150/100) for three main comparisons of pharmacokinetic properties: (1) age difference (within age group), (2) dose proportionality (child-to-adolescent within dose), and (3) gender differences (female-to-male within dose and age group). Point estimates and 90% CIs of the ratios were calculated with the arithmetic and least-squares means and SDs of the numerator and denominator groups.

The secondary objective comparing pharmacokinetic parameters between adolescents and adults was addressed by a meta-analysis comparing pharmacokinetic data from adolescents receiving fluvoxamine 150 mg b.i.d. with pharmacokinetic data from adults receiving fluvoxamine 150 mg b.i.d. from a previous study (Solvay Pharmaceuticals, Inc., unpublished, 1999). The multiple-dose pharmacokinetics of fluvoxamine in healthy male and female subjects ($n = 16$) were assessed. Pharmacokinetic results from adolescents and adults were compared by constructing a 90% CI (bioequivalence criteria) from an ANCOVA.

RESULTS

Subjects

Forty-three subjects, 20 children (8 females and 12 males) and 23 adolescents (12 females and 11 males) were enrolled in the study and received one or more doses of fluvoxamine. Primary diagnoses included OCD, depression, social phobia, and posttraumatic stress disorder. Six subjects were excluded from the pharmacokinetic analysis due to protocol violations. In addition, two subjects experienced AEs, and one subject withdrew before pharmacokinetic sampling. Therefore, 34 subjects were included in the pharmacokinetic analysis. Female and male subjects were fairly evenly distributed (44% female in the child group and 50% female in the adolescent group). The mean age for child and adolescent subjects included in the pharmacokinetic sample was 9.4 and 14.1 years, respectively. The mean weight was 94.4 lb for children and 132.5 lb for adolescents. The mean height was 54.9 in. for children and 64.8 in. for adolescents. The majority of children were Tanner staged 1 (69%) and 2 (25%). Sixty-two percent of adolescent subjects were Tanner stage 3 or higher.

Pharmacokinetic Results

Age Differences. To compare children with adolescents, mean values of key pharmacokinetic parameters were adjusted using a statistical model equation incorporating gender, age, Tanner stage, and body weight. Key pharmacokinetic parameter results are shown in Table 1. Mean serum concentrations were markedly higher in children compared with adolescents at each common dose level. Apparent oral clearance was consistently lower in children at all dose levels. Likewise, adjusted mean $C_{\text{max}}$, $C_{\text{min}}$, and $AUC_{0–12}$ values were consistently higher in children compared with adolescents at all dose levels. Statistically significant differences between children and adolescents were seen at the 50 mg b.i.d. administered dose level (100 mg/day) for CL/F, $C_{\text{max}}$, $C_{\text{min}}$, and $AUC_{0–12}$.

Figures 1 and 2 display mean plasma fluvoxamine concentration-time profiles over 12 hours of sampling for children and adolescents at each dose level. Statis-
tically significant differences in concentration-time profiles are observed in children compared with adolescents at 50 mg b.i.d. Large differences in concentration-time profiles are also apparent in children compared with adolescents at other dose ranges; however, the data are not statistically significant (likely owing to the high variability of interindividual pharmacokinetic parameter values and the small number of subjects).

**Dose Proportionality.** Dose proportionality was assessed by examining changes in pharmacokinetic behavior of the drug as a function of dose. For this evaluation, C\text{max}, C\text{min}, and AUC\text{0–12} values were normalized for dose and CL/F was normalized for body weight. Mean values of key pharmacokinetic parameters were adjusted using a statistical model equation incorporating dose, gender, Tanner stage, and body weight. In children, CL/F values decreased as a function of increasing dose. Differences in adjusted CL/F between the dose ratios 50/25 mg and 100/25 mg were statistically significant ($p \leq 0.05$). However, the dose ratio for 100/50 mg was not statistically significant,

### TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg)</th>
<th>Group (n)</th>
<th>Mean</th>
<th>SD</th>
<th>Adjusted Mean</th>
<th>Pair</th>
<th>Ratio (%)</th>
<th>90% CI on Ratio</th>
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<tr>
<td>CL/F (L/hr)</td>
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<td>25</td>
<td>C (16)</td>
<td>50.91</td>
<td>32.56</td>
<td>44.68</td>
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<td>57.58</td>
<td>32.2–102.8</td>
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<td>C (15)</td>
<td>30.38</td>
<td>23.73</td>
<td>20.34</td>
<td>50 C/A</td>
<td>36.61</td>
<td>18.0–74.5</td>
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<td>134.27</td>
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<td>C (10)</td>
<td>21.20</td>
<td>14.56</td>
<td>19.36</td>
<td>100 C/A</td>
<td>58.29</td>
<td>28.9–117.6</td>
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<td>57.25</td>
<td>64.13</td>
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<td>C\text{max} (ng/mL)</td>
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<td>93.5–261.9</td>
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<td>170.58</td>
<td>182.45</td>
<td>50 C/A</td>
<td>270.29</td>
<td>137.9–529.9</td>
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<td>A (17)</td>
<td>70.39</td>
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<td>318.56</td>
<td>371.47</td>
<td>100 C/A</td>
<td>170.49</td>
<td>89.3–325.6</td>
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<td>A (17)</td>
<td>233.12</td>
<td>133.84</td>
<td>217.89</td>
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<tr>
<td>AUC\text{0–12} (ng · hr/mL)</td>
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<td>C (16)</td>
<td>549.3</td>
<td>366.6</td>
<td>410.1</td>
<td>25 C/A</td>
<td>173.67</td>
<td>97.3–310.2</td>
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<td></td>
<td>A (18)</td>
<td>229.9</td>
<td>137.2</td>
<td>236.1</td>
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<tr>
<td>50</td>
<td>C (15)</td>
<td>2,236.4</td>
<td>1,677.9</td>
<td>1,801.6</td>
<td>50 C/A</td>
<td>273.20</td>
<td>134.2–556.3</td>
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<td>A (17)</td>
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<td>100</td>
<td>C (10)</td>
<td>5,211.3</td>
<td>3,417.6</td>
<td>3,785.9</td>
<td>100 C/A</td>
<td>171.54</td>
<td>85.0–346.1</td>
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<td>A (17)</td>
<td>2,401.8</td>
<td>1,436.9</td>
<td>2,207.0</td>
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*Note: C = children; A = adolescents; CI = confidence interval; CL/F = oral clearance adjusted for the fraction of drug absorbed; C\text{max} = maximal plasma concentrations; AUC\text{0–12} = area under the plasma concentration-time curve for 0 to 12 hours.*

* $p \leq 0.05$.

**Fig. 1** Mean plasma concentration-time profiles in children at all administered dose levels.

**Fig. 2** Mean plasma concentration-time profiles in adolescents at all administered dose levels.
likely due to the smaller sample of children \((n = 10)\) who completed sampling at 100 mg b.i.d. dosing. Adolescents showed trends of decreasing CL/F as the dose increased. For CL/F (corrected for body weight), a 19% decrease occurred as the administered dose increased from 25 to 50 mg b.i.d. \((p > .05)\), a 44% decrease from 50 to 100 mg b.i.d. \((p < .05)\), but essentially no change in adjusted CL/F from 100 to 150 mg b.i.d. This apparent lack of change at the higher dose may be due to the high variability of the data as well as decreasing numbers of subjects at the 150 mg b.i.d. dose level \((n = 13)\). No changes in \(T_{\text{max}}\) were seen with increased dose in children or adolescents.

Fluvoxamine pharmacokinetics were nonlinear in children and adolescents in the dose range studied; disproportional increases in mean \(C_{\text{max}}\), \(C_{\text{min}}\), and AUC\(0–12\) were evident with proportional dose increases. The confidence intervals indicated interindividual parameters in children and adolescents that were highly variable. Although adolescents demonstrated statistically significant nonlinear pharmacokinetics, the overall extent of disproportional concentration increase over time was greater in children. A similar pattern was seen for \(C_{\text{min}}\); however, \(C_{\text{min}}\) was not significantly higher when the 150/100 mg administered doses were compared \((n = 13)\) in adolescents. When 50 mg administered doses were used as the reference for comparison with the 100 mg administered dose, the 90% CIs suggested only marginally significant change in CL/F, dose-normalized \(C_{\text{max}}\), and dose-normalized AUC\(0–12\).

**Gender Differences.** In children, females consistently had higher mean plasma concentrations of fluvoxamine than males at all dose levels. Female children also had consistently lower mean CL/F values and consistently higher \(C_{\text{max}}\), \(C_{\text{min}}\), and AUC\(0–12\) compared with male children. Adjusted mean values for clearance were at least twice as low in female children compared with male children. In addition, \(C_{\text{max}}\), \(C_{\text{min}}\), and AUC\(0–12\) were at least twice as high in female than in male children. Figure 3 shows the mean plasma fluvoxamine concentration-time profiles over the 12-hour sampling for males and females receiving 25 mg b.i.d. Gender differences were statistically significant at the 25 mg b.i.d. dose. When male and female children are examined separately, the fluvoxamine concentration-time curve in male children receiving 25 mg b.i.d. appears similar to the fluvoxamine concentration-time curves for both male and female adolescents. In contrast, the fluvoxamine concentration-time curve for females was increased compared with the fluvoxamine concentration-time curves for both male and female adolescents. No differences between genders were seen for \(T_{\text{max}}\) values. Normalization of the pharmacokinetic parameters for body weight had no impact on the results of gender comparison data. In adolescents, no gender differences in pharmacokinetic parameters were apparent. Results were similar when adolescent pharmacokinetic parameters were normalized for body weight.

**Adolescents Versus Adults.** Adolescent data from this study were compared with adult data from a previous study (Solvay Pharmaceuticals, Inc., unpublished, 1999) in which subjects underwent pharmacokinetic sampling after receiving fluvoxamine 300 mg/day (150 mg b.i.d.). Comparison of the mean plasma concentration-time profiles from the two populations suggested little difference between the pharmacokinetic behavior of fluvoxamine in adolescents and adults. Figure 4 shows the mean plasma fluvoxamine concentration-time profiles over 12 hours of sampling for adolescents and adults on 150 mg b.i.d. However, the adjusted CL/F value in adolescents was approximately
50% greater than in adults. After body weight normalization, CL/F remained greater in adolescents compared with adults. This difference was not noted for \( C_{\text{max}} \), \( C_{\text{min}} \), or \( \text{AUC}_{0-12} \).

**Metabolizer Status.** Dextromethorphan/dextrorphan ratios were determined in 39 subjects. One subject was identified as a slow metabolizer. All 34 subjects in the pharmacokinetic sample were classified as extensive metabolizers. As a result, no analysis was conducted to determine pharmacokinetic parameter differences related to metabolizer status.

**Safety Results**

Forty-three subjects were enrolled in the study and received at least one dose of fluvoxamine. The majority of children (85%) and adolescents (78%) enrolled were exposed to study medication between 29 and 56 study days.

**Adverse Events.** AEs reported by four or more children included pharyngitis (30%), headache (25%), asthenia, abdominal pain, somnolence, nervousness, and rhinitis (20% each). AEs reported by four or more adolescents included headache (39%), infection (30%), asthenia (22%), and pain, somnolence, and nausea (17% each). More children (90%) than adolescents (65%) experienced AEs related to study medication. Female children reported more AEs than male children, female adolescents, and male adolescents. The latter three groups reported similar rates of AEs.

The majority of AEs related to fluvoxamine were rated as mild or moderate in severity. Eleven subjects (seven children and four adolescents) reported AEs rated as severe and probably related to fluvoxamine. Four subjects (three female children and one male child) discontinued the study due to AEs related to fluvoxamine. These AEs included hypomanic activation (one male), insomnia (two females), and dizziness, asthenia, and nausea (one female). No subjects reported a severe AE attributed to fluvoxamine.

**Adverse Events and Exposure.** To explore a possible relationship between AEs and exposure, fluvoxamine dose level and key AEs related to fluvoxamine treatment were plotted against the \( C_{\text{max}} \) and \( \text{AUC}_{0-12} \) values from pharmacokinetic data associated with the same dose level. Key AEs of interest were asthenia, headache, insomnia, nausea, somnolence, and vomiting. Pharmacokinetic parameters from all subjects who experienced the key AEs were compared with all subjects who did not experience the events. In no case was there a clear relationship between \( C_{\text{max}} \) or \( \text{AUC}_{0-12} \) and the occurrence of the key AEs or the severity of the key AEs. More adolescents \((n = 18)\) than children \((n = 8)\), and more females \((n = 18)\) than males \((n = 8)\) appeared to have a key AE associated with either \( C_{\text{max}} \) or \( \text{AUC}_{0-12} \) values. Twelve female adolescents and six male adolescents had key AEs; six female children and two male children had key AEs. Female children reported more AEs compared with male children, and there was a trend in which more female children discontinued the study due to AEs. The children who discontinued due to AEs did not demonstrate higher fluvoxamine exposure than children who remained in the study.

**Other Safety Results.** From baseline to termination, there were no clinically relevant changes in physical examination, vital signs, ECG, or clinical laboratory assessment in either the child or adolescent age groups. None of the concomitant medications taken by patients in the study were considered to have had any impact on safety parameters.

**DISCUSSION**

In this fluvoxamine pharmacokinetics study, children had significantly higher fluvoxamine exposure compared with adolescents at every dose level tested. In contrast, adolescents and adults appeared to have similar fluvoxamine exposure. These exposure data are consistent with data suggesting that children have greater pharmacokinetic exposure than adolescents (or adults) treated with nefazodone (Findling et al., 2000) and buspirone (Salazar et al., 2001). These data are inconsistent with data suggesting that children had less exposure than adolescents treated with paroxetine (Findling et al., 1999) and benzodiazepines (Coffey et al., 1983). Female children account for the majority of increased fluvoxamine exposure demonstrated in children in this study. When analyzed separately, male children had fluvoxamine exposure similar to that of adolescents and adults.

Explanations for the increased fluvoxamine exposure in children in this study include attribution to statistical error or methodological error or the presence of an undetermined pharmacokinetic factor related to development that contributes to differences in fluvoxamine exposure. The easiest explanation for these pharmaco-
kinetic results may be due to statistical error, which may or may not be associated with the small sample size of female children in the study. However, such robust differences in means when comparing these small sample sizes suggest otherwise. No statistical outliers among the female children explain the increased fluvoxamine exposure compared with adolescents, adults, and male children.

A methodological error in detection of slow metabolizers could be suspected because only one slow metabolizer was detected in the study (no slow metabolizer was detected in the sample included in pharmacokinetic analysis), which seems too rare (but feasible) given a genotype with a 5% prevalence. Failure to detect actual slow metabolizers could erroneously eliminate one potential explanation for differences in pediatric exposure to fluvoxamine: genetic polymorphism of 2D6. Decreased single-dose paroxetine clearance in pediatric subjects was found to correlate with slow metabolizer status of 2D6 (Findling et al., 1999), which metabolizes paroxetine and is also inhibited by paroxetine. The absence of outliers by site, age, and gender in this study suggest that errors in detecting genetic polymorphism of 2D6 were not a factor in the observed pediatric exposure differences in this study. Furthermore, the alternate explanation that genetic polymorphism occurred in all female subjects and no male subjects is unlikely.

An Undetermined Pharmacokinetic Factor Related to Age or Sex?

The U.S. Food and Drug Administration thought these data valid enough to make changes in pediatric dosing suggestions for the product insert of Luvox® (Solvay Pharmaceuticals, Inc.). If these data are valid, the most likely explanation for the increased exposure in female children involves a yet undetermined pharmacokinetic factor in females, children, or female children that contributes either to increased fluvoxamine exposure before puberty or relatively decreased fluvoxamine exposure after puberty. Interestingly, male adults showed higher fluvoxamine exposure than female adults (Harter et al., 1998), in direct contrast to these pediatric fluvoxamine exposure data.

Differences in blood flow, volume of distribution, and hormone effects in males and females are potential factors. Differences in circulating hormones related to age and sex are unlikely candidates because circulating hormones that could displace (and consequently increase measured fluvoxamine levels) are not significantly different for females until adolescence. It seems just as unlikely that highly protein-bound hormones could displace enough fluvoxamine (approximately 75% protein bound) to cause increased fluvoxamine exposure. Because female adolescents have fluvoxamine exposure similar to that of adults, male children, and male adolescents, a hypothetical pharmacokinetic factor could be expressed during childhood and then be “turned off” during adolescence.

Fluvoxamine is believed to be metabolized primarily through the CYP2D6 isozyme, whereas fit is a potent inhibitor of CYP1A2, CYP3A4, and CYP2C19 but not 2D6. Genetic polymorphism results in metabolic variability for 2D6 and to a lesser extent for CYP2C19, but it does not result in metabolic variability for any of the other known CYP450 isoenzymes. Even if isoenzymes other than 2D6 are involved in a secondary metabolic pathway of fluvoxamine, they would have a limited impact on the metabolism of fluvoxamine compared with 2D6. Children and adolescents showed evidence of nonlinear pharmacokinetics, consistent with pharmacokinetic data on adults treated with fluvoxamine (Spigset et al., 1998).

Limitations

This study was neither designed to detect nor powered to detect gender differences within age group, so the fluvoxamine exposure data in female children must be interpreted with caution. Similarly, this was not a dose finding study, so dosing implications for fluvoxamine in children and adolescents are speculative. The diminishing number of subjects who tolerated full-dose titration made dose-related pharmacokinetic findings less robust, revealing readily apparent trends but statistically significant differences at only select dose levels. In addition, there was great interindividual variability in pharmacokinetic parameters related to multiple-dose fluvoxamine treatment, which is consistent with other pharmacokinetic studies. Because all subjects in the pharmacokinetic sample in this study were extensive metabolizers (CYP2D6 isoenzyme), these data may not directly apply to patients who are CYP2D6 slow metabolizers. Clinical outcome measures were not conducted in this study; therefore, fluvoxamine exposure could not be correlated with clinical effect.
Clinical Implications

As expected from previous clinical trials of fluvoxamine (and other SSRIs) in pediatric subjects, fluvoxamine was well tolerated by children and adolescents in this study. Fluvoxamine doses as high as 200 mg/day in children and 300 mg/day in adolescents presented no safety concerns. Although females reported more AEs attributed to fluvoxamine and demonstrated higher fluvoxamine exposure, there was no correlation between the occurrence and severity of key AEs in the study and either serum concentration or total exposure to fluvoxamine. No safety issues preclude the use of 200 mg fluvoxamine in children or 300 mg in adolescents, although children (particularly females) may be more susceptible to the AEs of fluvoxamine regardless of dose. Although there are currently no data correlating exposure of fluvoxamine (or any SSRI) and efficacy, adolescents may require fluvoxamine doses as high as 300 mg/day to achieve optimal exposure. Although the results of this study are insufficient to conclude that children require lower doses of fluvoxamine, the observed increased exposure in female children calls for care in selection of dose.

Research Implications

A replication study involving more female children is recommended to validate these fluvoxamine exposure findings in specific populations based on gender and age. Further pharmacokinetic studies should involve genotyping of 2D6 instead of phenotyping to increase the accuracy of slow metabolizer detection, and slow metabolizers should be included. Although it would be noteworthy to identify a correlation between pharmacokinetic parameters and clinical effect or AEs such as activation symptoms, the “effect compartment” and “AE compartment” of fluvoxamine requires better delineation to account for differences in efficacy and AEs reported in different populations.

Data from other disciplines may inform age-related differences in pharmacokinetic parameters based on serotonin blood levels and/or serotonin genes (Persico et al., 2000). Increased fluvoxamine exposure in children may help explain the better response of children compared with adolescents receiving similar daily doses in the pediatric OCD treatment study by Riddle et al. (2001). Age was not a moderating factor of efficacy in the fluvoxamine anxiety treatment study (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2003).

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REFERENCES


Research Units on Pediatric Psychopharmacology Anxiety Study Group