Pharmacokinetics of Methylphenidate in Preschoolers with Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: The aim of this study was to compare the pharmacokinetics of immediate-release methylphenidate (MPH) in preschool and school-aged children with attention-deficit/hyperactivity disorder (ADHD).

Methods: Preschool children 4–5 years (n = 14) and school-aged children 6–8 years (n = 9) with diagnoses of ADHD were titrated to an effective dose of MPH based on parent, teacher, and clinician ratings in a protocol specified by the Preschoolers with ADHD Treatment Study (PATS) and then attended a laboratory school where the single morning dose of immediate release MPH was administered. Blood samples for measurement of MPH concentrations were obtained predose, and at 1, 2, 4, and 6 hours postdose. A nonlinear model was used to derive three pharmacokinetic (PK) values for analysis: Peak plasma concentration (C\text{max}), half-life (t\text{1/2}), and clearance (CL).

Results: The two groups did not differ in the mean mg dose of MPH (p = 0.33), or in the weight-adjusted mg/kg dose (p = 0.20). Dose-normalized C\text{max} was significantly higher (p = 0.003), and clearance was significantly slower (p = 0.0002) in preschool than in school-aged children.

Conclusions: In this sample, age significantly affected absorption and metabolism of MPH, so that preschool children had greater exposure than school-aged children to the same weight-adjusted dose. These data suggest additional studies should be performed to characterize age-related differences in PK properties of MPH that may inform practitioners about dosing strategies based on the age and size of children being treated.
INTRODUCTION

METHYLPHENIDATE (MPH) is the most commonly prescribed psychotropic medication for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, including the subgroup of preschool children, even though it does not have Food and Drug Administration (FDA) approval for use in children under 6 years of age. Because of the increasing use of stimulant medication in this group, the National Institute of Health Consensus Development Conference on the Diagnosis and Treatment of Attention-Deficit Hyperactivity Disorder (1998) identified a need for studies of the risks and benefits associated with treatment of preschool-aged children with stimulant medication, including pharmacokinetic (PK) properties to evaluate age-related effects on drug absorption and metabolism, pharmacodynamic (PD) properties to evaluate onset, peak, and duration of behavioral effects, dose–response characteristics, and side effects related to short- and long-term exposure to stimulants.

Although some controlled clinical trials have been performed with preschool children with ADHD as subjects, to our knowledge there have been no prior PK studies of MPH in this age group. Recently, age-related differences in the PK properties of MPH were documented in an industry-sponsored comparison of Concerta™, a controlled-release formulation of MPH, in school-aged and adolescent subjects (Food and Drug Administration, 2005). The finding indicated that clearance of MPH depended on age and was greater (faster) in adolescents, which was sufficient to warrant a change in the package insert for Concerta™ to guide clinical treatment of different age groups (McNeil 2004).

The primary objective of this small, preliminary study was to compare the plasma concentrations and associated pharmacokinetic parameters (maximum concentration, half-life, and clearance) after administration of a clinically-titrated morning dose of MPH in preschool and school-aged children with ADHD from one of the six sites of the Preschoolers with ADHD Treatment Study (PATS) who were evaluated in the context of a laboratory school protocol (Swanson et al. 2000; Wigal and Wigal 2006) and to relate the findings of the literature in age-related effects on the PK properties of MPH.

METHODS

Single site of the PATS

Challenges were encountered in the groundbreaking PATS protocol that required some modifications as it was implemented. One modification was to restrict the overall PATS to preschool children, because recruitment challenges and limited funding made the evaluation of school-aged children impractical. The University of California, Irvine (UCI) site had accelerated recruitment, and school-aged children were entered into the PATS protocol before it was modified. Another modification was to eliminate the laboratory school component from the protocol, which was intended for implementation at each of the six sites after the titration phase (Kollins et al. 2006). Accelerated recruitment at the UCI site (Greenhill et al. 2006), prior experience with the laboratory school protocol (Swanson et al. 2003; Wigal and Wigal, 2006), and extra funding to one of the UCI investigators made it feasible to implement this component partially at the UCI site.

The PK study was an add-on component to the PATS protocol, but the design requirements of a school-aged comparison group and the implementation of the laboratory school protocol precluded execution at all sites. Therefore, it was a single-site study implemented at one of the PATS sites with a small sample size. In this paper we present preliminary information from a small sample to guide future work on age-related differences in the PK properties of MPH.

Subjects

The subjects for this study met the general entry criteria for the multisite PATS described in detail by Greenhill et al. (2006) and followed the same overall protocol also described in detail by Kollins et al. (2006), which will not be
repeated here. The additional entry criteria and protocol methods of this single-site PK study will be described in detail.

Children were required to meet the criteria for ADHD, Combined Type or Predominantly Hyperactive-Impulsive Type as defined by the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; diagnostic code 314.01) (American Psychiatric Association, 1994), to be between the ages of 36–65 months old (for the preschool groups) and 72–96 months old (for the school-aged group), and to be able to tolerate catheter insertion for the collection of blood samples to be used for the measurement of plasma concentrations of MPH.

In the overall PATS protocol (Kollins et al. 2006) subjects participated in prebaseline (3-week, open-label, lead-in) assessments of tolerability to doses of immediate release MPH from 1.25 mg to 7.5 mg, followed by a double-blind, placebo-controlled medication titration trial of those doses administered three times a day (t.i.d.), a parallel, between-group comparison of the best dose chosen during titration versus placebo, and a 10-month, open-label follow-up starting at the best dose with monthly clinic visits in which dose adjustments were allowed. For the single-site PK study, participants were given their morning dose of the clinically optimized t.i.d. MPH regimen established during the maintenance phase of the PATS.

Study design

This study was conducted at UCI in accordance with the principles of the Declaration of Helsinki and its amendments, and approved by the UCI Institutional Review Board. At a screening visit, parents provided written consent for their child’s enrollment, and all subjects provided either written or verbal assent. Subjects who met study eligibility requirements were scheduled to attend the Saturday session for PK data collection. Figure 1 shows the laboratory classroom schedule for the PK study day. Subjects were instructed not to eat or to take study medication prior to coming to the laboratory school. Subjects were prescribed EMLA® cream (2.5% lidocaine and 2.5% prilocaine) for local, topical anesthesia at the catheter insertion site, and parents were instructed to apply this immediately prior to arrival for maximal numbing action on site. Children were fed a standardized, regular breakfast consisting of cereal, 1% milk, and fresh fruit at about 7 a.m. and were given their morning dose of MPH by 8 a.m. Thus, food intake was controlled to exclude potential effects of food on the PK properties of MPH (Chan et al. 1983; Gonzalez et al. 2002).

The PK samples were obtained via a catheter placed in the antecubital vein in each subject’s forearm. Subjects participated in various distracter techniques including viewing “I Spy” books and listening to songs on tape during catheter insertion and PK sampling. Blood samples prior to dosing and at four times after dosing (1, 2, 4, and 6 hours) were collected into EDTA Vacutainer® tubes. The blood samples were processed immediately by centrifugation, and the plasma samples were stored at approximately −20°C before frozen shipment on dry ice to National Medical Services (NMS), where they were analyzed by high-performance liquid chromatography/mass spectrometry (LC/MS) to determine the concentrations of d-threo- and l-threo-MPH, as well as d- and l-ritalinic acid, the principal MPH metabolites (data on file at NMS). The quantification limits of the assay were as follows: For l-threo-MPH in plasma, the lower limit of quantification (LLOQ) defined as the lowest concentration achieving an acceptable coefficient of variation (C.V.) of ±20% at the LLOQ was a value of 0.5 ng/mL and the upper limit of quantification (ULOQ) was defined as the lowest concentration achieving an acceptable C.V. of ±15% at the ULOQ with a value of 100 ng/mL; for ritalinic acid in plasma, the C.V.’s were similar in value, with the LLOQ of 5.0 ng/mL and the ULOQ of 400 ng/mL.

PK profiles were analyzed by noncompartmental methods (WinNonlin version 4.1, Pharsight Corporation). The maximum MPH plasma concentration (C_{max}) and time to reach the maximum concentration (T_{max}) were recorded as the observed values. The elimination half-life was estimated using the terminal portion of the concentration profile, and the area under the concentration-time curve ex-
trapolated to infinity (AUC<sub>inf</sub>) was calculated by a linear trapezoidal method. The apparent clearance is the clearance (CL) divided by the fraction (F) of the dose determined by bioavailability (F) or (CL/F), and in both absolute and weight-adjusted terms the apparent clearance was estimated as the quotient of the dose and AUC<sub>inf</sub>. Four subjects in the school-aged group had insufficient data to allow estimation of a half-life or AUC<sub>inf</sub>. PK parameter estimates for the school-aged and preschool groups were based on prospective estimates of sample size and were compared using a two-tailed <i>t</i>-test. Because the sample sizes for the preschool (<i>n = 14</i>) and school-aged (<i>n = 9</i>) children were small, for the reasons outlined above, we present effect sizes with confidence intervals of our comparisons as well as significance levels. Estimates of effect size can be used to make informed estimates about the sample size and power requirements for future studies.

<table>
<thead>
<tr>
<th>Hour</th>
<th>Time</th>
<th>Activity</th>
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<th>Time</th>
<th>Activity</th>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Lunch</td>
</tr>
<tr>
<td>0</td>
<td>9:00</td>
<td>Class #0</td>
<td>12:15</td>
<td>1:20</td>
<td>Vitals</td>
</tr>
<tr>
<td></td>
<td>9:30</td>
<td>Dosing</td>
<td></td>
<td></td>
<td>Nap/Quiet Time</td>
</tr>
<tr>
<td></td>
<td>9:40</td>
<td>Snack</td>
<td>12:30</td>
<td>2:00</td>
<td>Outdoor Free Play</td>
</tr>
<tr>
<td></td>
<td>9:50</td>
<td>Outdoor Play</td>
<td></td>
<td>2:30</td>
<td>Snack</td>
</tr>
<tr>
<td></td>
<td>10:20</td>
<td>Vitals</td>
<td>2:40</td>
<td>3:20</td>
<td>Indoor Activity</td>
</tr>
<tr>
<td>1</td>
<td>10:30</td>
<td>PK &amp; Class #1</td>
<td>3:20</td>
<td>4:00</td>
<td>RECESS Play</td>
</tr>
<tr>
<td></td>
<td>11:00</td>
<td>Indoor Free Play</td>
<td></td>
<td>4:15</td>
<td>Clean Up/Prizes</td>
</tr>
<tr>
<td></td>
<td>11:10</td>
<td>Vitals</td>
<td>4:30</td>
<td></td>
<td>Dismissal</td>
</tr>
<tr>
<td>2</td>
<td>11:30</td>
<td>PK &amp; Class #2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12:00</td>
<td>RECESS Play</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIG. 1. Study day schedule.
RESULTS

Patients

Basic demographic information including gender and ethnicity for the two age groups are shown in Table 1. Of 18 preschool children who consented to the study, a total of 14 subjects were enrolled, 1 subject would not comply with study procedures on the practice day preceding the PK study day and was withdrawn from participation, 1 subject withdrew consent due to excessive fear of needles, and 2 subjects participated in classroom measurements only on the PK day to maintain adequate classroom size, with no blood samples collected. Of 10 school-aged subjects who consented to the study, 9 were enrolled. One child was ill and unable to attend the study day. Of the preschool children, 1 child received 2.5 mg, 8 children received 5 mg, 4 children received 7.5 mg, and 1 child received 10 mg of MPH. Of the school-aged children, 2 children received 2.5 mg, 2 children received 5 mg, 1 child received 7.5 mg, and 4 children received 10 mg of MPH.

As expected, the preschool-aged group was significantly ($p < 0.0001$ for each) younger (5.3 versus 7.4 years of age), shorter (112 versus 129 cm), and weighed less (19 versus 28 kg) than the school-aged group (see Table 1).

Pharmacokinetic effects

Table 2 shows the comparison of weight, clearance, and other variables of the preschool-aged and school-aged children who completed the PK protocol. A total of 115 blood samples were collected across the multiple observations within each of the subjects. $d$-MPH was quantified in all samples; $l$-MPH typically was negligible and could not be quantified by analysis as is typically found in PK studies of oral administration (Srinivas et al. 1992; Srinivas et al. 1993; Quinn et al. 2004), which accounts for the maximum bioavailability (50%) of oral doses of the racemic mixture of MPH (see Chan et al. 1983). Ritalinic acid concentrations were high and quantifiable in all samples. The ratio of the $d$-ritalinic acid to $d$-MPH was the same for all samples and, therefore, only the MPH is presented and discussed here. There was considerable variability in the estimated PK parameters ($%CV$ ranging from 32 to 72). At time 0 hour, when blood levels of MPH were not expected due to the short half-life of the drug and the overnight washout period, only 1 out of 23 subjects had a quantifiable blood sample, and this value was very small (<0.5 ng/ml).

The range of titrated dose levels (i.e., 2.5–7.5 mg t.i.d.) was identical for both age groups (see Fig. 2). The average total morning dose was 5.89 mg for preschoolers and 6.94 mg for the school-aged group.

Table 1. Summary of Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Preschool children (n = 14)</th>
<th>School-aged children (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Male</td>
<td>64.3</td>
<td>44.4</td>
</tr>
<tr>
<td>% Female</td>
<td>35.7</td>
<td>55.6</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Combined</td>
<td>71.4</td>
<td>100</td>
</tr>
<tr>
<td>% Hyperactive/impulsive</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.3 years</td>
<td>7.4 years</td>
</tr>
<tr>
<td>Range</td>
<td>4–6 years</td>
<td>7–8 years</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19.2 kg</td>
<td>28.3 kg</td>
</tr>
<tr>
<td>Range</td>
<td>14.6–22.7 kg</td>
<td>21.2–39.8 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>112 cm</td>
<td>129.43 cm</td>
</tr>
<tr>
<td>Range</td>
<td>98–119 cm</td>
<td>121–140 cm</td>
</tr>
<tr>
<td>Dose level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.0 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Range</td>
<td>2.5–10.0 mg</td>
<td>2.5–10.0 mg</td>
</tr>
</tbody>
</table>
school-aged children (see Table 2), but this difference was not significant in a comparison of the absolute mg dose \( (p = 0.33) \) or the relative mg/kg dose adjusted for weight \( (p = 0.20) \).

As shown in Fig. 3, clearance and dose-normalized \( C_{\text{max}} \) were strongly correlated with age. This was expected, because weight is a function of age and apparent clearance and dose-normalized \( C_{\text{max}} \) would be expected to vary directly with weight (and correspondingly with age).

The dose-normalized maximum concentration was significantly \( (p = 0.003) \) higher for the preschool-aged group \( (1.72 \text{ L}^{-1}) \) than the school-aged group \( (1.1 \text{ L}^{-1}) \). Similarly, the dose-normalized AUC was significantly higher \( (p = 0.009) \) for the preschool-aged group \( (0.012 \text{ L/hour}) \) than for the school-aged group \( (0.0047 \text{ L/hour}) \).

### Table 2. Comparisons of Preschoolers and School-Aged Subjects

<table>
<thead>
<tr>
<th></th>
<th>Preschoolers</th>
<th>School-aged</th>
<th>Difference in 95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5.33 ± 0.56</td>
<td>8.00 ± 0.56</td>
<td>4.77</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>19.2 ± 1.9</td>
<td>28.3 ± 5.8</td>
<td>9.54</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>5.89 ± 1.9</td>
<td>6.94 ± 3.3</td>
<td>0.42</td>
</tr>
<tr>
<td>Dose/weight (mg/kg)</td>
<td>0.311 ± 0.09</td>
<td>0.252 ± 0.13</td>
<td>0.20 (−0.44, 1.25)</td>
</tr>
<tr>
<td>CL/F (L/hour)</td>
<td>99.5 ± 44</td>
<td>232.6 ± 75</td>
<td>2.52</td>
</tr>
<tr>
<td>CL/F weight (L/hour per kg)</td>
<td>5.12 ± 1.9</td>
<td>7.91 ± 1.6</td>
<td>1.52</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>457.8 ± 210</td>
<td>737.8 ± 296</td>
<td>1.2</td>
</tr>
<tr>
<td>t1/2 (hour)</td>
<td>3.62 ± 2.7</td>
<td>2.18 ± 0.3</td>
<td>−0.53</td>
</tr>
<tr>
<td>AUC (ng.h/mL)</td>
<td>75.2 ± 54</td>
<td>41.8 ± 22</td>
<td>−0.32</td>
</tr>
<tr>
<td>AUC/D (hour/L)</td>
<td>0.012 ± 0.005</td>
<td>0.0047 ± 0.002</td>
<td>−1.54</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>10.2 ± 5.0</td>
<td>7.6 ± 4.2</td>
<td>0.55</td>
</tr>
<tr>
<td>1,000 C(_{\text{max}})/D (1/L)</td>
<td>1.72 ± 0.5</td>
<td>1.10 ± 0.3</td>
<td>−1.44</td>
</tr>
<tr>
<td>T(_{\text{max}}) (hour)</td>
<td>2.57 ± 0.9</td>
<td>2.56 ± 1.1</td>
<td>−0.01</td>
</tr>
</tbody>
</table>

CL = clearance; F = fraction of dose determined by bioavailability; AUC = area under the curve; V = volume; L = liter; D = dose normalized. CL/F = apparent clearance; V/F = apparent volume of distribution; t\(_{1/2}\) = half-life; T\(_{\text{max}}\) = time to maximum plasma concentration; C\(_{\text{max}}\), maximum plasma concentration.

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**FIG. 2.** Identical range of titrated dose levels by age group. ▲ Preschoolers ● School-aged.
The half-life for MPH was 3.82 hours for the preschool-aged group and 2.18 hours for the school-aged group. This difference was not statistically significant ($p = 0.46$), but the effect size was $0.69$, $(-1.70, 0.38)$.

The preschool-aged group had a significantly ($p < 0.0001$) decreased apparent clearance of MPH than the school-aged group (99.5 L/hour compared to 232.6 L/hour), and the effect size was $2.52$ ($1.13, 3.68$). When controlled for weight, the clearance for the preschool-aged group (5.12 L/hour per kg) was still lower than for the school-aged group (7.91 L/hour per kg), and this difference remained statistically significant ($p = 0.01$), and the effect size was 1.52 ($0.33, 2.57$).

**DISCUSSION**

To our knowledge, this is the first study to present a preliminary comparison of PK characteristics of MPH in preschool children with ADHD to another age group. The primary finding of this preliminary study is the slower clearance of MPH in the group of preschool-aged children compared to the same PK parameter in school-aged children. Of the various PK pa-
rameters, clearance is thought to be the most relevant to clinical practice because it serves as a surrogate for dose-adjusted exposure. Clearance represents the sum of individual clearance processes [hepatic (biliary and metabolic), renal, etc.] and is expected to change in relation to factors that influence these processes. Our estimates of clearance are consistent with the few reports in the literature, which provide estimates of clearance in school-aged children from a small sample in a traditional repeated measures PK protocol: $n = 4$, 5.47 L/hour per kg (Hungund et al. 1979) and a large sample in a population PK protocol with one measure from each individual: $n = 213$, 5.4 L/hour per kg (Shader et al. 1999). These values as depicted in Fig. 4 fall between the values we observed from our preschool (5.12 L/hour per kg) and school-aged (7.91 L/hour per kg) groups constrained to narrow age ranges.

In an early publication about the PK properties of MPH, comparison of school-aged children with adults suggested that clearance was not related to age (Wargin et al. 1983). However, recent evidence suggests that apparent clearance of MPH does vary with age (Food and Drug Administration, 2005). This led to a change in the package insert for Concerta®, a controlled-release formulation of MPH, which now states, “Increase in age resulted in increased apparent oral clearance” (CL/F) (58% increase in adolescents compared to children (McNeil 2004). Some of these differences could be explained by body weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.” The data from the present study are consistent with this statement and suggest that younger and smaller preschool-aged children may have greater exposure to MPH than older and heavier school-aged children at similar doses. A similar PK effect was reported for mixed amphetamine salts extended release (MAS SR; Adderall XR®) between child, adolescent, and adult age groups (Kramer et al. 2005).

The faster clearance of MPH by school-aged children compared to preschool children may be due to the increase in size and maturation of the metabolic enzymes in the older group. There are many implications of these ontogenetic differences, but little information is published in the literature to answer basic questions about this (Coffey 1983). Ginsberg et al. (2002) reviewed PK parameters of children and adults for 45 therapeutic drugs with a wide range of indications and PK factors and analyzed for systematic differences across age groups. They noted, in general, shorter half-lives with more rapid clearance in the older child age groups as seen in the present study. However, information on age differences in the PK properties of MPH was not included in their review, because there was very little data published on the PK properties of MPH (particularly in young children).

Another possible explanation of the difference in clearance may be that preschool-aged children may have less fully developed metabolic enzymes such as esterases and organ functioning than school-aged children, which would result in a slower clearance in the younger age group. This result is counterintu-

FIG. 4. Mean MPH dose in relation to body weight.
itive, but has been reported with other drugs with increasing age in the lower age range. An example of a drug that shows an increase in clearance from preschool to school-aged children is the antiepileptic drug, topiramate (Dahlin and Ohman 2004).

In the present study, the mean dose for the school-aged group was higher (but not significantly, due to the small sample size), but the MPH plasma concentration was lower than for the preschool-aged group. Because the doses were titrated for both groups to achieve good clinical effect, this suggests that younger and lighter children may require higher plasma concentrations for maximum efficacy than older and heavier children. However, there are at least two speculations to consider. In the PATS, the doses included in the titration process were limited to 7.5 mg t.i.d. or less, compared to 20 mg t.i.d. or less in the Multimodality Treatment Study of ADHD or MTA. The degree of efficacy (ES) was related to dose in the PATS, so at high doses the relationship of efficacy to plasma level may have been different. Also, the finding in the current study is based on systemic concentrations of MPH, not brain levels or central nervous system effects at the site of action of MPH, which is primarily blockade of the dopamine transporter (DAT) in the striatum (Volkow 1995; Volkow et al. 2002). The age- and weight-related differences in transport into the brain might result in similar brain levels of MPH and similar degree of DAT inhibition despite age- and weight-related differences in plasma concentrations in MPH.

The MPH dose and plasma concentration data presented in the current investigation also are consistent with published reports on MPH. Shader et al. (1999) characterized the population PK of b.i.d. and t.i.d. MPH in children with ADHD. In their study, the mean age of the children ranged from 5.4 to 18 years, and their weights ranged from 17 to 142 kg. The mean total daily dose was 33.6 mg (range = 10–60). In their study, they also noted that the total daily dose increased with body weight for both the b.i.d. and t.i.d. dosing regimens. In contrast, the plasma MPH concentrations decreased with body weight ($p > 0.1$ for the b.i.d. regimen and $0.1 (p < 0.05$ for the t.i.d. regimen). These results are consistent with the observations noted in the present study. Additionally, the clearance value of 5.4 L/hour per kg reported by Shader et al. (1999) is comparable to that noted in the present investigation.

PK variables (such as distribution and clearance, which affect optimal dose titration of drugs) are related to body water, muscle mass, organ blood flow, and organ function (Rowland and Tozer 1989). Statistically controlling for body weight would be expected to cause nonsignificant PK effects unless it reflects some other physiological organ function—maturation of metabolic enzymes systems involved in metabolism or central processing changes in site utilization of the drug. The metabolism of MPH is through hydrolysis/de-esterification and some oxidation (Markowitz et al. 2003), but the hydrolyzing enzymes such as human carboxylesterase CES1A1 (Zejin et al. 2004) may have a different pattern in this process in preschoolers than in school-aged children. If these age-related differences do exist, it may have implications for pharmacologic treatment (including MPH) of preschoolers with ADHD.

Preschool children have higher circulating levels of MPH than school-aged children for the same weight-adjusted dose. The half-life of MPH was nonsignificantly longer for preschool-aged children than school-aged children in this study probably due to the small sample size. The design of the present study could not address whether more sleep problems or loss in appetite correlated with higher plasma MPH concentrations later in the day because all of these children already were maintained on an efficacious dose. This would have to be addressed in future studies with laboratory school assessments in preschoolers occurring during initial exposure to stimulant treatment.

**LIMITATIONS**

The primary limitation of this study is the small number of subjects in each age group. Some reasons for the small sample (discussed above) were due to recruitment issues related to accumulating a group of participants in the laboratory school protocol and the age of the children. This issue should be addressed in future studies to ensure a larger sample size.
Another limitation was the number of blood samples per subject and the short time interval covered by these samples. This limitation was related to the young age of the preschool children, which made participation in the usual 8- to 12-hour laboratory school day impractical. Another primary limitation was the relatively short sampling period (i.e., only 6–7 hours following oral dosing) used in this study. This provides the minimum required for a reasonable estimate of $t_{1/2}$—approximately one half-life following the expected value of $T_{\text{max}}$. Given these two primary limitations, the estimates of the half-life and clearance must be interpreted cautiously. The preliminary findings from this initial study need to be replicated with larger samples to establish generalizability of the results.

Also, as typical in studies of the influence of age on PK, this was a cross-sectional study of different children at separate points in development, and, therefore, does not reflect how an individual may change with age. The results from this study in small groups of children merit further investigation in larger studies, in which children are followed from an early age to adulthood and PK characteristics are measured at multiple time points during development.

**CLINICAL IMPLICATIONS**

The primary finding of this preliminary study suggests that preschool children with ADHD may absorb, distribute, metabolize, or eliminate MPH differently than school-aged children with ADHD. The full report of the efficacy data from the PATS (Greenhill 2006) suggests that clinical titration may result in similar absolute doses but higher relative (mg/kg) doses in preschool children than in school-aged children. This, along with possible differences in PK characteristics, may suggest differences in dose and dosing rate for preschool children compared to school-aged children. The clinician is faced with two questions when prescribing IR MPH for a child with ADHD: (1) “What dose is required for this patient?” (which typically is chosen based on titration) and (2) “How often and when should the dose be administered?” (which is traditionally set at 3- to 4-hour intervals for b.i.d. and t.i.d. regimens).

Are the same plasma concentrations needed in preschool-aged children and school-aged children to achieve the same clinical effect? The present study suggests not, since both age groups were titrated to maximum clinical effect (based on subjective ratings) but had different plasma concentrations. The findings from the present study suggest that preschool-aged children may need higher concentrations to achieve the same effect as school-aged children. These findings also are consistent with the clinical practice of generally using absolute MPH dose rather than weight-adjusted (mg/kg) doses. If the range of doses is about the same for preschool and school-aged children, then the smaller size (and volume of distribution) will result in a higher concentration of MPH in plasma. However, as discussed earlier in this paper and in Kollins et al. (2006), the absolute dose as well as the effect size for efficacy for this end point (derived from the crossover titration trial) were lower for the preschool-aged group than is typical for school-aged children with ADHD treated with MPH.

Is the same dosing rate appropriate for preschool and school-aged children? The present study suggests not, because the concentration at the titrated dose appears to be higher and the clearance decreased in preschool children than in school-aged children. On the basis of the standard use of PK information, for a given average concentration, the dosing rate would be proportional to clearance.

Practitioners may want to consider using a different target dose regimen of MPH (stated as a range of absolute or mg/kg doses) for preschoolers and school-aged children due to the possible age-related differences in clearance. This would be similar to and consistent with the different targets for school-aged children and adolescents, which has been noted by the FDA (Food and Drug Administration 2005) and has been acknowledged in the package insert for the most commonly prescribed formulation of MPH in current clinical practice (McNeil 2004), which noted that clearance is related to weight and may suggest adjustments in the dosing regimen. The FDA (Food
and Drug Administration, 2005) report provided information on estimates of clearance for school-aged children (243 L/hour), adolescents (384 L/hour), and adults (497 L/hour), which provide a context for the estimates of clearance for the present study for preschool children (99 L/hour) and school-aged children (232 L/hour). Even though these estimates depend on the assay used for determining MPH concentrations and other factors that may vary across studies, this does clearly indicate that clearance of MPH in plasma is related to age and/or size and varies considerably from early childhood (about 100 L/hour) to adulthood (about 500 L/hour).

Additional information on the PK characteristic of MPH is needed to use this basic information to guide clinical practice for selecting and optimizing the doses for the treatment of all ages of children diagnosed with ADHD.

DISCLOSURES

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REFERENCES

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