Understanding the Central Pharmacokinetics of Spheroidal Oral Drug Absorption System (SODAS) Dexmethylphenidate: A Positron Emission Tomography Study of Dopamine Transporter Receptor Occupancy Measured With C-11 Altropane

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ABSTRACT

Objective: Pediatric studies of the long-acting formulation (spheroidal oral drug absorption system [SODAS]) of the isomer dexmethylphenidate have shown a dose-dependent efficacy through 12 hours. However, there are no studies of central nervous system (CNS) dopamine transporter occupancies.

Method: Eighteen healthy volunteers underwent positron emission tomography (PET) imaging with C-11 altropane before and after administration of oral doses of SODAS dexmethylphenidate. Each group of 6 subjects received 1 of 3 doses (20 mg, 30 mg, 40 mg) before PET imaging at 1, 8, 10, 12 (20 mg and 30 mg), or 1, 8, 10, and 14 (40 mg) hours after dosing. Transporter occupancy was calculated by standard methods. The study was conducted from January 2007 through December 2007.

Results: For all doses, plasma dexmethylphenidate levels and CNS dopamine transporter occupancies were greatest at 8 hours and decreased over time at 10, 12, and 14 hours. Plasma dexmethylphenidate levels were correlated to dose ($P < .003$). Mean plasma levels were ≥ 6 ng/mL to at least 8 hours with 20 mg (5.7 ng/mL), 10 hours with 30 mg, and 12 hours (extrapolated) with 40 mg. Dopamine transporter occupancies in the right caudate were 47% at 8 hours with 20 mg, 42% at hour 10 with 30 mg, and 46% (extrapolated) at hour 12 with 40 mg. Dopamine transporter occupancy was significantly correlated with plasma concentration of dexmethylphenidate ($P < .001$).

Conclusions: These results confirm the study hypothesis that central dopamine transporter occupancy parallels peripheral pharmacokinetic findings in orally administered long-acting dexmethylphenidate in later hours after administration.

Trial Registration: ClinicalTrials.gov identifier: NCT00593138

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Stimulants have been shown to be effective in the treatment of attention-deficit/hyperactivity disorder (ADHD).[1] Studies have shown that longer duration treatment is often preferable to shorter treatment,[2] and recent guidelines advise longer duration treatment in the appropriate patients.[3] Accordingly, new delivery systems for stimulants have evolved to provide various degrees of clinical coverage across the day.

One of such new formulations is the long-acting formulation of dexmethylphenidate. This compound has been formulated using the spheroidal oral drug absorption system (SODAS) double bead technology. Clinical studies of SODAS dexmethylphenidate have demonstrated efficacy in children and adults with ADHD.[4,5] Although analog classroom studies of SODAS dexmethylphenidate have demonstrating efficacy as early as 30 minutes and through 12 hours,[6–8] there are no studies of central nervous system (CNS) pharmacokinetic properties of SODAS dexmethylphenidate. Understanding the central nervous system pharmacokinetic properties is critical for elucidating the brain effects of medicines for ADHD of different lengths of action and to corroborate estimated duration of action of individual compounds used in the treatment of ADHD based on peripheral pharmacokinetic data.

It has been estimated that racemic methylphenidate is effective when the CNS dopamine transporter occupancy is 50% or greater.[9] This estimation was derived from comparison of the average plasma dexmethylphenidate plasma levels of effective treatment of racemic methylphenidate in children (6 ng/mL)[10–12] and the CNS dopamine transporter occupancy at that plasma dexmethylphenidate level in normal adult volunteers at peak (2 hours [6 ng/mL in plasma ≈ 50% CNS dopamine transporter occupancy]).[9] A recent pharmacokinetic study of SODAS dexmethylphenidate in normal adults recorded average plasma dexmethylphenidate levels of greater than or equal to 6 ng/mL in plasma through 8 hours for 20 mg, 10 hours for 30 mg, and 12 hours for 40 mg.[13]

The primary aim of this study was to evaluate whether the central pharmacokinetics of dopamine transporter receptor occupancy (using positron emission tomography [PET] and C-11 altropane) parallel peripheral pharmacokinetic parameters of onset and duration of orally administered SODAS dexmethylphenidate. The doses of SODAS dexmethylphenidate (20, 30, 40 mg) chosen, have been shown to be efficacious in a randomized, placebo-controlled study in adults with ADHD.[5] We hypothesized that central dopamine transporter occupancy would parallel peripheral pharmacokinetic findings.

METHOD

Eighteen healthy human subjects between 18 and 55 years were sequentially recruited from advertisements. Subjects gave their informed consent after the procedures and possible side effects were fully explained. Massachusetts General Hospital institutional review board approval was obtained. All subjects were right-handed and in good health. All subjects had a complete medical and

psychiatric history and physical examination before imaging. None had any *DSM-IV* Axis I disorders, including ADHD as well as current or past drug or alcohol abuse. In addition, none had a history of exposure to psychotropic medicines (including stimulants) or tobacco. In women, inquiry about the subject's current reproductive status was also made. In addition, all subjects had an electrocardiogram, full blood count, blood chemistries, and a urinalysis (including drug screen and, in women, a pregnancy test). The study is registered at clinicaltrials.gov (identifier: NCT00593138).

Clinical Points

- The need to examine the relationship of plasma levels and dopamine transporter (DAT) occupancies in early and late times after administration is warranted given the concern about possible tachyphylaxis with a long-acting methylphenidate.
- Plasma levels and the DAT occupancies were consistent with dose and a spheroidal oral drug absorption system (SODAS) formulation designed to release 2 equal pulses of dexmethylphenidate 4 hours apart.
- The relationship of DAT occupancy to plasma dexmethylphenidate levels was similar at later hours in this long acting formulation to that previously reported at peak in an immediate-release formulation.

Procedures

Subjects underwent PET imaging before and after administration of oral doses (20, 30, and 40 mg of dexmethylphenidate). Six subjects (3 men and 3 women) were randomly assigned to receive each dose level (20, 30, and 40 mg) of dexmethylphenidate in an open-label protocol. Subjects were instructed not to eat 8 hours before and 2 hours after dosing. For those 6 subjects randomly assigned to receive open-label 20 mg or 30 mg of dexmethylphenidate, repeat PET scans determined dopamine transporter occupancy at 1, 8, 10, and 12 hours' postdose (compared to baseline). For those 6 subjects randomly assigned to receive 40 mg of dexmethylphenidate, repeat PET scans determined dopamine transporter occupancy at 1, 8, 10, and 14 hours' postdose. Venous blood was drawn for quantification of plasma dexmethylphenidate concentration 1 hour prior to scanning, at the hour of scanning, and at the completion of the scan. The study was conducted from January 2007 through December 2007.

Positron emission tomography images were acquired using an HR+ (CTI, Knoxville, Tennessee) PET camera. The primary imaging parameters of the HR+ camera are in-plane and axial resolution of 4.5 mm full width at half maximum, 63 contiguous slices of 2.42 mm separation. Images were acquired in 3D mode and reconstructed using filter back projection with a ramp filter of 4.00 mm. Photon attenuation measurements were made with rotating pin sources containing 68Ge.

C-11 Altropane is a highly suitable ligand for dopamine transporter imaging because it has relatively high dopamine transporter affinity (Km: 12 nM), high dopamine transporter selectivity, and low nonspecific binding.[14] For each scan, approximately 5 mCi of C-11 altropane was injected intravenously over 30 seconds and serial PET images acquired. Dynamic image collection started at the same time as the infusion, and images were acquired in 15-second frames for the first 2.0 minutes, in 1-minute frames for the next 4.0 minutes, and in 2-minute frames for the last 27 frames, 60 minutes in all. All projection data were corrected for nonuniformity of detector response, dead time, random coincidences, and scattered radiation. Regions of interest representing the striatum (left and right caudate nucleus and left and right putamen) and cerebellum were drawn manually on PET images. This procedure was repeated for all slices in which the structures were visualized at full intensity (away from edge slices). For each frame, regions of interest of like structures were computed to yield mean striatal and cerebellar time activity curves. We determined that the reference (cerebellum) time activity curves were not affected by the dopamine transporter inhibitor. Time activity curves from the regions with dopamine transporter bindings were fitted to a simplified reference region model[15] to calculate binding potential for each region. These binding potentials are used to calculate the cold drug percentage occupancy with the following formula: percentage occupancy = $100 \times \{[\text{binding potential (baseline)} - \text{binding potential (postdrug)}]/\text{binding potential (baseline)}\}$.

To estimate the plasma dexmethylphenidate level required to occupy 50% of the dopamine transporter receptor sites, the percentage of dopamine transporter occupancy (P) was linearized by plotting the logarithm of P divided by (100 – P) versus the logarithm of the plasma level of dexmethylphenidate (ng/mL). The linear regression permitted the determination of the plasma dexmethylphenidate level associated with 50% occupancy of the dopamine transporter, which, in turn, corresponds to the 0.0 value on the y-axis in a scattergram showing the slope of the relationship between plasma dexmethylphenidate concentration and dopamine transporter occupancy.

Statistical Analysis

Categorical data were analyzed by χ^2 analysis, continuous parametric data by analysis of variance (ANOVA) with post hoc pairwise comparisons (Scheffe), or unpaired *t* test and the rank sum test for nonparametric data. Associations between continuous variables were evaluated using Pearson correlations. We chose a significance level of .05. All tests were 2-tailed.

RESULTS

Pharmacokinetic Profile of SODAS Dexmethylphenidate

Plasma dexmethylphenidate levels were greatest at 8 hours after drug administration (for all doses) and decreased

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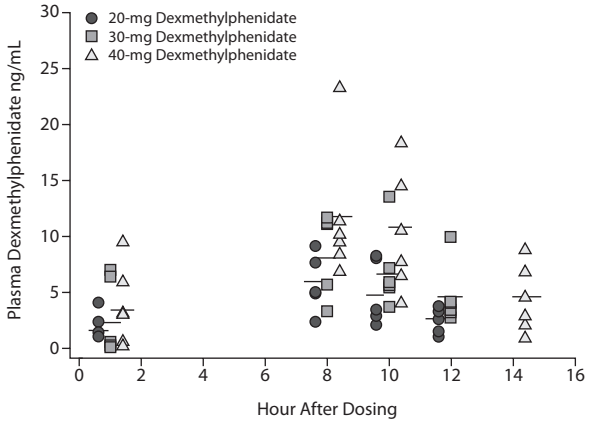
Figure 1. Plasma Pharmacokinetics of Dexmethylphenidate[a]



[a]20- and 40-mg values offset to aid visualization. The horizontal line represents the mean for each horizontal group of data (by dose and hour).

Table 1. Plasma Dexmethylphenidate Levels

Time Point, h	20 mg (n = 6), Mean ± SD, ng/mL	30 mg (n = 6), Mean ± SD, ng/mL	40 mg (n = 6), Mean ± SD, ng/mL	Statistic
1	2.0 ± 1.3[a]	2.4 ± 3.4	3.7 ± 3.5	$F_{2,14} = 0.5$, $P < .61$
8	5.7 ± 2.4	8.2 ± 3.7	11.6 ± 5.9	$F_{2,15} = 2.9$, $P < .09$
10	4.7 ± 2.7	6.9 ± 3.4	10.3 ± 5.4	$F_{2,15} = 2.9$, $P < .09$
12	2.5 ± 1.1[a]	4.5 ± 2.7	NA	$F_{1,9} = 2.6$, $P < .14$
14	NA	NA	4.5 ± 2.9	

[a]n = 5.
Abbreviation: NA = not available.

over time at 10, 12, and 14 hours (Figure 1). In a multivariate analysis, plasma dexmethylphenidate levels were correlated to dose ($t_{66} = 3.15$, $P < .003$) but not weight ($t_{66} = 1.13$, $P < .30$). At any given time after drug administration, the plasma dexmethylphenidate levels were greater for higher doses (20, 30, and 40 mg). Omnibus (ANOVA) statistical comparisons of dexmethylphenidate levels between all doses were not statistically significant at any hour. In relationship to a cutoff of 6 ng/mL, the plasma dexmethylphenidate levels were less than 6 ng/mL at hour 1 for all doses. In contrast, mean plasma levels were greater than or equal to 6 ng/mL to at least 8 hours with 20 mg (5.7 ng/mL), 10 hours with 30 mg, and 12 hours (extrapolated) with 40 mg (Table 1).

Dopamine Transporter Occupancy in the Striatum by Orally Administered Dexmethylphenidate

The pattern of CNS dopamine transporter occupancies was (mostly) similar to that of the plasma dexmethylphenidate levels. The highest values were comparable at 1 and 8 hours, and there was a gradual decrease at 10, 12, and 14 hours. At each hour, CNS dopamine transporter occupancies increased with increasing dose (20, 30, and 40 mg) (Figure 2A–D). At 20 mg, the highest occupancies were 46%–48%; the lowest, 27%–31% (12 hours). At 40 mg, the highest occupancies were 62%–67%; the lowest, 36%–40% (14 hours). Although the study was not powered to statistically examine differences in occupancies between doses, differences between 40 mg and 20 mg were statistically significant at 8 hours in the right caudate ($t_{1,10} = 3.82$, $P < .005$) as well as between 40 mg and 20 mg at 8 hours ($t_{1,10} = 2.81$, $P < .02$) and between 30 mg and 20 mg at 12 hours ($F_{1,10} = 3.23$, $P < .009$) in the left caudate (Table 2). Using a 50% occupancy cutoff resulted in a mean dopamine transporter occupancy that was less than 50% at 8 hours for 20 mg and greater than or equal to 50% up to at least 8 hours with 30 mg (right and left caudate) and 10 hours with 40 mg (Table 2). Alternatively, a 40% occupancy cutoff resulted in a mean dopamine transporter occupancy that was greater than or equal to 40% to at least 8 hours with 20 mg and 10 hours with 30 mg and 14 hours (right caudate) with 40 mg (Table 2).

The Relationship of Dexmethylphenidate to Dopamine Transporter Occupancy in Orally Administered Dexmethylphenidate

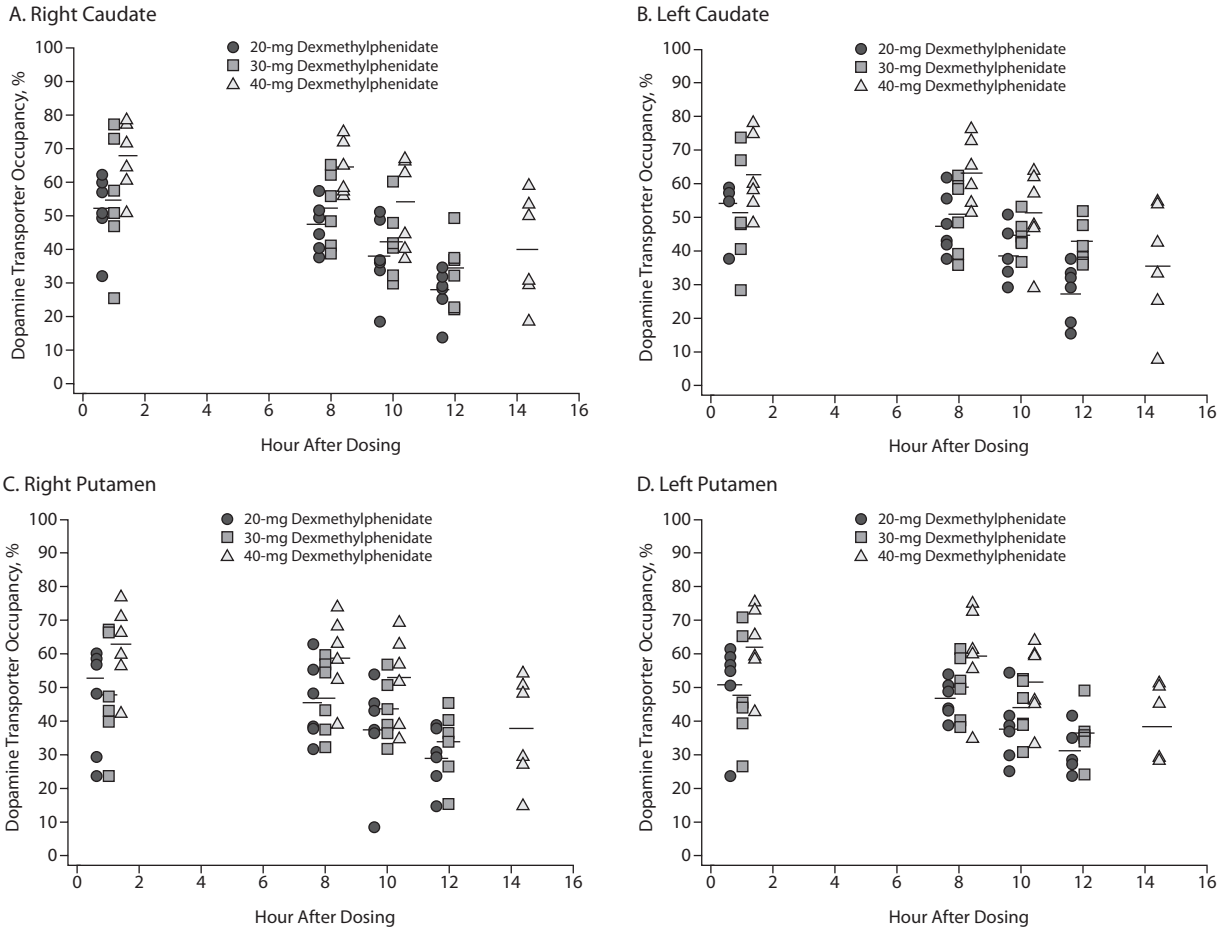
For oral long-acting dexmethylphenidate (SODAS dexmethylphenidate), dopamine transporter occupancy was significantly correlated with plasma dexmethylphenidate concentration (correlation coefficient = 0.79, $t = 9.17$, $P < .001$) (Figure 3A). A multivariate analysis revealed that, after the 1-hour measurement was removed, the relationship of plasma dexmethylphenidate to dopamine transporter occupancy was not affected by time after administration ($t_{50} = 0.18$, $P < .86$). We used a log transformation of dopamine transporter data (similar to the analysis of dopamine transporter findings by Volkow et al[9]) to find that, for oral long-acting dexmethylphenidate (SODAS dexmethylphenidate), a plasma dexmethylphenidate concentration of 4.0 ng/mL was associated with a 50% blockade of dopamine transporter. However, the plasma concentration associated with 50% blockade at 1 hour (0.7 ng/mL) was about 10% of those at later hours (average of 6.7 ng/mL, hours 8–14; Figure 3B).

DISCUSSION

The primary aim of this study was to evaluate whether the central pharmacokinetics of dopamine transporter occupancy match peripheral pharmacokinetic properties of dexmethylphenidate when using oral doses of SODAS dexmethylphenidate known to be efficacious in adults with ADHD.[5] Consistent with a medium-acting methylphenidate compound, results showed that both plasma dexmethylphenidate levels and dopamine transporter occupancies of SODAS dexmethylphenidate peaked at 8 hours and declined thereafter. Dopamine transporter occupancies (but not plasma dexmethylphenidate levels) of SODAS dexmethylphenidate were consistent with a rapid onset of action. These results confirm the study hypothesis that central dopamine transporter occupancy parallels peripheral pharmacokinetic findings in orally administered long-acting dexmethylphenidate in later hours after administration.

Our study did not examine the relationship of dose to peak plasma levels and peak dopamine transporter occupancies for methylphenidate. Volkow et al[9] reported on that

Figure 2. Dopamine Transporter Occupancy by Hour and Dose[a]



[a]20- and 40-mg values offset to aid visualization. The horizontal line represents the mean for each horizontal group of data (by dose and hour).

relationship previously. In contrast, this study examined the relationship of dose, plasma level, and dopamine transporter occupancy at early and later time periods selected by comparison to other studies that examined the time course of clinical efficacy. Previous pharmacodynamic studies had shown that, in children, this formulation has an onset of behavioral action at 1 hour, and efficacy continued to 11 hours for 20 mg and to 12 hours for 30 mg (again in children).[6–8] Thus, we examined plasma levels and dopamine transporter occupancies at 1 hour as well as at 8 hours (and after) for each dose. Since studies suggested that higher doses might be behaviorally active beyond 12 hours, we measured plasma levels and dopamine transporter occupancies at 14 hours for the 40-mg dose.

Mean dopamine transporter occupancies were greater at higher doses at each time period but few were statistically significant, underscoring the substantial interindividual differences in the pharmacokinetic of the drug in the brain and in plasma. While average rates of response are greater with higher doses of methylphenidate in adults[16] and children,[3] there is a good deal of individual variability.[17] As discussed by Volkow and Swanson,[18] some of the variability of response may be due to the weak relationship of plasma level and dopamine transporter occupancy to changes in extracellular dopamine. While weight is thought to have some effect on plasma levels,[17] there was no relationship in our study. Our group recently reported a series of cases in which failure to respond to relatively higher doses corresponded to relatively low blood levels.[19] Thus, it may be that blood levels would be of clinical utility in patients who have unusual responses to methylphenidate.

Dexmethylphenidate dopamine transporter occupancies were significantly correlated with plasma concentration of dexmethylphenidate. The relationship of plasma dexmethylphenidate to dopamine transporter occupancy is not affected by time after removing the 1-hour measurements. The relationship between dopamine transporter occupancy and peripheral pharmacokinetic at later times is similar to that reported in previous studies at 2 hours.[9] Reasons for the anomalous 1-hour results are unknown. More work needs to be done to examine the relationship of dopamine transporter occupancy and plasma dexmethylphenidate levels at early hours.

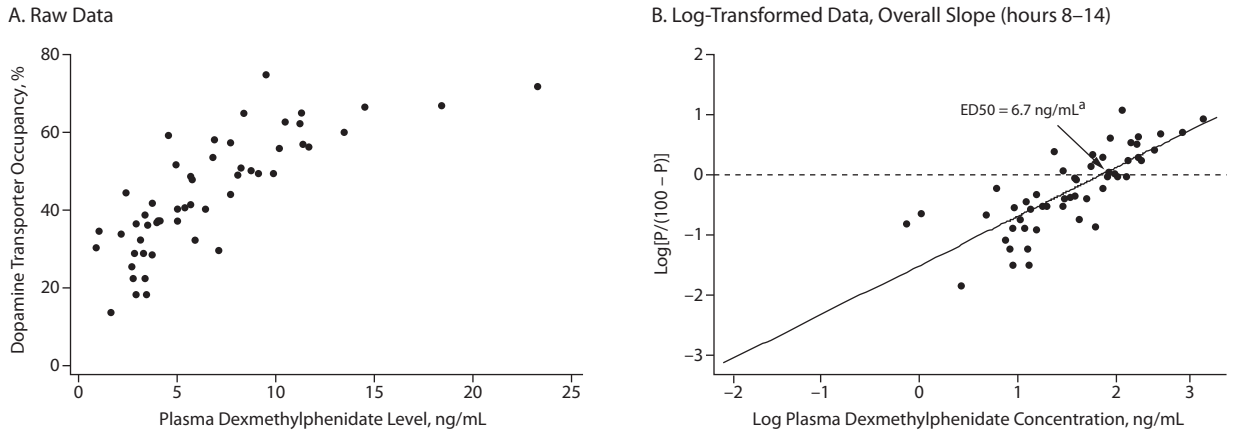
These PET results are consistent with the SODAS formulation that was designed to release 2 pulses of dexmethylphenidate 4 hours apart. Similarly, our results showing that

Table 2. SODAS Dexmethylphenidate Dopamine Transporter Percentage Occupancy

Time Point, h	20 mg (n = 6), Mean ± SD	30 mg (n = 6), Mean ± SD	40 mg (n = 6), Mean ± SD	Statistic
Right caudate				
1	51.8 ± 10.9	55.0 ± 18.8	66.8 ± 10.6	$F_{2,15} = 1.9$, $P < .19$
8	46.5 ± 7.4	51.8 ± 10.9	63.5 ± 8.0[a]	$F_{2,15} = 5.7$, $P < .02$
10	37.3 ± 11.8	41.9 ± 11.0	52.7 ± 13.8	$F_{2,15} = 2.5$, $P < .12$
12	27.0 ± 7.3	33.3 ± 10.2	NA	$F_{1,10} = 1.5$, $P < .25$
14	NA	NA	39.9 ± 16.4	NA
Left caudate				
1	54.0 ± 8.2	51.2 ± 16.8	62.6 ± 11.8	$F_{2,15} = 1.3$, $P < .31$
8	48.1 ± 9.1	50.7 ± 11.1	63.6 ± 9.9[b]	$F_{2,15} = 4.0$, $P < .04$
10	39.2 ± 8.0	44.6 ± 5.7	51.3 ± 13.0	$F_{2,15} = 2.5$, $P < .12$
12	27.8 ± 8.8	42.2 ± 6.4	NA	$F_{1,10} = 3.2$, $P < .009$
14	NA	NA	36.4 ± 18.3	NA
Right putamen				
1	52.0 ± 11.8	47.9 ± 16.7	62.2 ± 12.3	$F_{2,15} = 1.7$, $P < .22$
8	45.8 ± 12.0	47.2 ± 11.3	59.2 ± 12.4	$F_{2,15} = 2.3$, $P < .13$
10	37.4 ± 15.5	42.9 ± 9.4	52.4 ± 13.6	$F_{2,15} = 2.0$, $P < .17$
12	29.1 ± 9.2	32.8 ± 10.8	NA	$F_{1,10} = 0.4$, $P < .53$
14	NA	NA	37.4 ± 15.9	NA
Left putamen				
1	51.0 ± 14.0	48.6 ± 16.8	62.4 ± 12.0	$F_{2,15} = 1.6$, $P < .24$
8	46.3 ± 5.6	50.1 ± 9.4	59.8 ± 14.5	$F_{2,15} = 2.7$, $P < .11$
10	37.7 ± 10.2	43.3 ± 8.6	51.3 ± 11.7	$F_{2,15} = 2.6$, $P < .11$
12	30.5 ± 6.6	35.8 ± 8.1	NA	$F_{1,10} = 1.6$, $P < .24$
14	NA	NA	38.7 ± 11.4	NA

[a]Versus 20 mg: $t_{1,10} = 3.82$, $P < .005$.
[b]Versus 20 mg: $t_{1,10} = 2.81$, $P < .02$.
Abbreviation: NA = not available, SODAS = spheroidal oral drug absorption system.

Figure 3. Plasma Dexmethylphenidate Level and Dopamine Transporter Occupancy



[a]ED50 represents the plasma dexmethylphenidate level required to occupy 50% of the dopamine transporter receptor sites.
Abbreviation: P = dopamine transporter occupancy.

plasma dexmethylphenidate levels peaked at 8 hours after SODAS dexmethylphenidate administration for all doses assessed and decreased at later hours are consistent with the design of the delivery system of this formulation.

Dopamine transporter occupancies observed at hours 8 to 14 were consistent with those predicted from the relationship of plasma dexmethylphenidate to dopamine transporter occupancy in studies using racemic dextro, levo methylphenidate.[9] Our hour 1 plasma levels were low and not consistent with the hypothesis that 6 ng/mL is a necessary threshold for efficacy. Our hour 1 plasma levels are different than other pharmacokinetic studies of SODAS dexmethylphenidate[13] for unknown reasons. In contrast, our dopamine transporter occupancies would imply that SODAS dexmethylphenidate might be effective at 1 hour. We know from a number of analog classroom studies that SODAS dexmethylphenidate is effective by 1 hour and even by one-half hour.[6–8] Reasons for the relative dissociation between hour 1 plasma levels and dopamine transporter occupancy are unknown. In contrast, the relationship between plasma levels and dopamine transporter occupancy for the later time periods are close to those reported previously.[9]

In the current study, dexmethylphenidate dopamine transporter occupancies were close but somewhat less than 50% out to the hours at which plasma dexmethylphenidate levels were ≥ 6 ng/mL. This profile is consistent with comparisons

of pharmacodynamics to pharmacokinetic in children and pharmacokinetic/dopamine transporter occupancy in adults using racemic dextro, levo methylphenidate. These latter studies estimated that a plasma dexmethylphenidate level of ~6 ng/mL corresponds to a dopamine transporter occupancy of approximately 50% at peak (2 hours), and these values are needed for clinical effectiveness. In the current study, dopamine transporter occupancies were 47% at 8 hours with 20 mg of SODAS dexmethylphenidate, 42% at hour 10 with 30 mg (Table 2), and 46% (extrapolated) at hour 12 with 40 mg. Taken together, the pattern of plasma dexmethylphenidate levels and dopamine transporter occupancies support the hypothesis that the duration of action of the SODAS dexmethylphenidate formulation is dose dependent. A recent analog classroom study of children demonstrated the dose-dependent duration of efficacy for SODAS dexmethylphenidate.[7]

Swanson et al[10] proposed a model in which an increasing plasma methylphenidate profile is necessary to avoid tachyphylaxis and maintain response. However, the comparison of response to pharmacokinetic profile at later, post-ingestion times reveals limitations to the ascending model. The methylphenidate formulation with the most prolonged pharmacokinetic pattern, osmotic controlled-release (OROS) methylphenidate, has a plasma time of maximal concentration (T_{max}) (in adults) of 6–7 hours[12,20] and a dopamine transporter occupancy T_{max} of 5 hours[21]; however, OROS methylphenidate is thought to be clinically effective for up to 12 hours.[10] Similarly, SODAS dexmethylphenidate (in adults) has a plasma T_{max} of 5.5 hours[13] and is thought to be clinically effective for up to 10 hours.

Aside from the first hour, the plasma concentration of dexmethylphenidate associated with a 50% dopamine transporter occupancy was 20% higher than that previously reported in a study of racemic (dextro, levo-methylphenidate) 6.7 ng/mL versus 5.6 ng/mL, for dexmethylphenidate (hours >1).[21] One possible interpretation of this finding is that in the racemic methylphenidate, a metabolite of levomethylphenidate may loosely attach to the dopamine transporter binding site in a manner that may block the imaging ligand without effectively blocking dopamine uptake. Thus, dopamine transporter occupancies in racemic studies could be a mixture of specific (functional) dopamine transporter blockade from dexmethylphenidate and nonspecific (nonfunctional) dopamine transporter interference from a metabolite of levomethylphenidate. Although more work is needed to test this hypothesis, there is clinical and preclinical evidence to support this possibility.[22–25] Future studies of changes in intrasynaptic dopamine may be necessary to investigate potential differences in the functional relationships of dopamine transporter occupancy between the dextro isomer and racemic methylphenidate.[26]

Our findings must be interpreted in light of the limitations of the study. We did not measure dopamine transporter occupancies before 1 hour. Peak occupancy occurs before 1 hour for intravenous but not oral administration of methylphenidate.[9] Continuous measurement of dopamine transporter occupancies from oral C-11 methylphenidate cannot be done in humans because of too much gastrointestinal radiation exposure with oral C-11 methylphenidate. Volkow et al[9] measured oral C-11 methylphenidate in a baboon and reported peak dopamine transporter occupancy of greater than 60 minutes for immediate-release methylphenidate. We would expect this to be true of SODAS dexmethylphenidate since the initial T-max for plasma is from 1.5 to 2 hours.[13]

While our results support the usefulness of examining dopamine transporter occupancies, there are limitations. Although we were able to calculate multiple measures of dopamine transporter occupancy at different times and doses, this study cannot establish the clinical meaning of those occupancies. As discussed above, currently the relationship of the dopamine transporter occupancy to clinical effectiveness is estimated by extrapolating effective plasma levels from pediatric pharmacokinetic/pharmacodynamics studies to plasma level/dopamine transporter relationships from adult pharmacokinetic (peripheral/CNS) studies of racemic methylphenidate. While the doses of SODAS dexmethylphenidate chosen have been shown to be efficacious in a randomized placebo-controlled study in adults with ADHD,[5] a more direct measure of pharmacokinetic (peripheral/CNS)/pharmacodynamics studies in adults is necessary to directly establish the relationship. The establishment of effective dopamine transporter occupancies would require an adult laboratory model to directly correlate dopamine transporter occupancy and efficacy at critical time periods. There have been several attempts to establish a reliable and validated laboratory model to measure pharmacodynamics in adults as has been established in children.[27,28] In addition, as discussed above, adult pharmacokinetic/pharmacodynamics studies will need to be done separately for isomeric and racemic methylphenidate formulations. Finally, studies of changes in intrasynaptic dopamine may more directly measure parameters of clinical utility.[26]

This study examined the relationship between peripheral and central pharmacokinetic properties of 3 doses of oral long-acting dexmethylphenidate (SODAS dexmethylphenidate). Plasma dexmethylphenidate levels and dopamine transporter occupancies were found to be internally consistent by dose and hour. The pattern of plasma dexmethylphenidate levels and dopamine transporter occupancies support the hypothesis that the duration of action of the SODAS dexmethylphenidate formulation is dose dependent. The relatively small difference in dexmethylphenidate-associated dopamine transporter occupancies between racemic dexmethylphenidate and those reported here may result from nonspecific interference from a metabolite of levomethylphenidate. Further work needs to be done to disentangle these issues.

Drug names: dexmethylphenidate (Focalin and others), methylphenidate (Daytrana, Ritalin, and others).

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