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Dose Proportionality and Steady-State Pharmacokinetics of Serdexmethylphenidate/Dexmethylphenidate, a Novel Prodrug Combination to Treat Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: The study was designed to determine (1) the pharmacokinetic (PK) profile of dexmethylphenidate (d-MPH) after oral administration of three dosage strengths of a new treatment containing d-MPH and a novel prodrug, serdexmethylphenidate (SDX); (2) the dose proportionality of the different SDX/d-MPH dosages; and (3) the steady-state PK profile of d-MPH and SDX after multiple dosing of SDX/d-MPH.

Methods: Twenty-three healthy volunteers (aged 18–55 years) under fasted conditions received in a crossover design SDX/d-MPH 26.1/5.2 mg (Treatment A), 39.2/7.8 mg (Treatment B), and 52.3/10.4 mg (Treatment C) for a total d-MPH hydrochloride equivalent dose of 20, 30, and 40 mg, respectively. After a 96-hour washout period, all participants received four consecutive daily doses of SDX/d-MPH 52.3/10.4 mg. Blood samples were collected for measurement of plasma d-MPH and SDX and for PK analysis.

Results: Administration of all three doses of SDX/d-MPH resulted in a rapid rise and slow decline in the plasma concentration of d-MPH. For Treatments A, B, and C, mean (± standard deviation) maximum concentrations (C_{max}) were 7.1 ± 2.1, 9.8 ± 2.8, and 13.8 ± 3.8 ng/mL, and overall exposures (AUC_{0-last}) were 97.2 ± 28.8, 142.5 ± 41.2, and 199.8 ± 57.2 h*ng/mL, respectively. Dose-normalized C_{max}, AUC_{0-last}, and AUC_{0-inf} for d-MPH were similar when comparing the high and low doses versus the middle dose. Power model regression analysis revealed that C_{max} and AUC_{0-inf} proportionally increased with an increase in SDX/d-MPH dose. In the multiple-dose study, d-MPH reached steady state before the third dose, and SDX after the first dose.

Conclusion: The PK profile of SDX/d-MPH is characterized by a rapid rise and a gradual decline in d-MPH concentration, with proportional C_{max} and AUC_{0-inf} across doses. The PK attributes of SDX/d-MPH may optimize symptom control from early morning to early evening, while the demonstrated dose proportionality may facilitate initial dose titration and ongoing dose adjustment.

Keywords: methylphenidate, pharmacokinetics, attention-deficit/hyperactivity disorder, stimulant, serdexmethylphenidate

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental condition characterized by inattention, impulsivity, and hyperactivity. A cross-sectional study conducted in 2016 assessed the prevalence of ADHD diagnosis among U.S. children between 2 and 17 years of age and found that an estimated 6.1 million children (9.4%) had ever received an ADHD diagnosis, and 5.4 million (8.4%) had the disorder at the time of the study (Danielson et al. 2018). Children with ADHD

typically present with difficulty in maintaining an appropriate level of attention and focus, which can impact cognitive and academic performance. Left untreated, ADHD has been shown to increase the risk for psychiatric disorders, antisocial behavior, poor physical health, and diminished socioeconomic status in adulthood (Shaw et al. 2012).

Due to variability in patient response to specific pharmaceutical agents, the quest for relief of ADHD symptoms spanning morning waking to early evening hours continues to drive research for new treatments for ADHD. Current pharmaceutical interventions used to treat ADHD include stimulants, such as amphetamine and methylphenidate (MPH), and nonstimulant agents such as atomoxetine and α_2-agonists. A meta-analysis comparing the efficacy and tolerability of various medications across all age groups identified MPH as the first choice to treat ADHD in children and adolescents (Cortese et al. 2018). MPH is a central nervous system stimulant that inhibits the reuptake of dopamine and norepinephrine, which is thought to improve sustained attention and focus (Volkow et al. 2002).

MPH is a racemic mixture of two enantiomers, dexmethylphenidate (d-MPH) and l-methylphenidate (l-MPH); however, studies conducted in animal models and humans have shown that the d-MPH isomer is the main pharmacological contributor to efficacy in ADHD treatment. When taken orally, the l-MPH isomer of MPH is stereoselectively metabolized in the liver, resulting in considerably lower plasma concentrations and activity than d-MPH (Quinn 2008).

Most once-daily extended-release MPH formulations have shown efficacy up to 12 hours postdose, but high interpatient variability in response to a given drug may result in less than optimal symptom management for certain periods of the day in some patients (Swanson and Volkow 2002, 2003; Coghill et al. 2013). For example, in evaluations of various formulations of MPH, some patients experienced better symptom control in the morning, with more limited symptom control in the evening (Brams et al. 2008; Muniz et al. 2008; Silva et al. 2008), while others experienced better control in the evening but less control of early morning symptoms (Whalen et al. 2006; Sallee 2015; Childress et al. 2020). New pharmacologic interventions that facilitate a rapid increase in d-MPH plasma concentrations that are maintained through the early evening hours may provide an option for more effective and sustained management of ADHD symptoms for a larger portion of patients.

Serdexmethylphenidate/d-MPH (SDX/d-MPH) was recently approved by the U.S. Food and Drug Administration (Azstarys™) for treatment of patients with ADHD. It contains a molar ratio of 70% of SDX (Supplementary Fig. S1A), a novel prodrug of d-MPH, and 30% of d-MPH. Azstarys is a Schedule II drug product due to the presence of d-MPH (Supplementary Fig. S1B). SDX, on the contrary, is a Schedule IV controlled substance as it has lower abuse potential than d-MPH (Drug Enforcement Administration 2021); however, SDX as a single entity is not currently marketed or approved by the U.S. Food and Drug Administration for any indication.

SDX is a classic prodrug in that it is pharmacologically inactive until converted to active d-MPH primarily in the lower gastrointestinal tract. d-MPH is the major active metabolite of SDX, and although the precise mechanism of this conversion is yet to be elucidated, there is no evidence of any new metabolic processes that affect breakdown of SDX or d-MPH into novel metabolites (Braeckman et al. 2022). SDX and its metabolites are not retained long term in any tissues (Braeckman et al. 2022). The objective of the current study was to evaluate the steady-state pharmacokinetic (PK) profile of d-MPH; the dose proportionality of SDX/d-MPH at 26.1/5.2, 39.2/7.8, and 52.3/10.4 mg dosage strengths (total equivalent doses of 20, 30, and 40 mg of d-MPH HCl, respectively); and the steady-state PK profiles of d-MPH and SDX after multiple doses of SDX/d-MPH in healthy adults.

Methods

Ethics

This study was conducted in accordance with clinical research guidelines established by the basic principles defined in the U.S. Code of Federal Regulations (21 CFR) Parts 50, 56, and 312; the ethical principles of the Declaration of Helsinki (and its amendments); and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. An institutional review board, IntegReview IRB, reviewed and approved the clinical study protocol and other study documents. The board is constituted, and operates in accordance with the principles and requirements described in the U.S. 21 CFR Part 56. All participants provided a signed written informed consent document before performing any baseline study-specific evaluations. The investigator/study site retained the original signed informed consent document and provided one copy of the document to all study participants.

Participants

Eligible study participants were healthy subjects between 18 and 55 years of age (inclusive) at screening. They included males and nonpregnant, nonbreastfeeding females and had a body mass index between 18 and 32 kg/m^2 (inclusive) and body weight between 50 and 100 kg.

Exclusion criteria included a history or the presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, among other factors. The complete list of inclusion and exclusion criteria is provided in the Supplementary Data S1.

SDX/d-MPH capsules

Study subjects received SDX/d-MPH capsules containing a 70:30 molar ratio of SDX and d-MPH, in the following dosages: Treatment A, 26.1 mg of SDX and 5.2 mg of d-MPH; Treatment B, 39.2 mg of SDX and 7.8 mg of d-MPH; Treatments C and D, 52.3 mg of SDX and 10.4 mg of d-MPH. The total dose for Treatments A, B, and C/D was equimolar to 20, 30, and 40 mg of d-MPH HCl, respectively.

Study design

The study was an open-label, randomized crossover design consisting of single-dose and multiple-dose phases. Study drug was administered orally to study participants under fasted conditions. For the single-dose treatment phase, all study participants received Treatment A (SDX/d-MPH 26.1/5.2 mg), Treatment B (SDX/d-MPH 39.2/7.8 mg), and Treatment C (SDX/d-MPH 52.3/10.4 mg) according to a randomization schedule in a crossover manner. Each treatment was separated by a 96-hour washout period and was administered on days 1, 5, and 9. After completion of the single-dose treatment phase plus another 96-hour washout period, all participants received multiple doses of Treatment D every 24 hours for 4 consecutive days (dose 1–4).

Blood sampling

A total of 86 blood samples were collected from each participant during the study. During single-dose treatment periods, blood sampling occurred predose and at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, 24, 36, 48, 60, and 72 hours postdose for each of the three dosage strengths of SDX/d-MPH. In the multiple-dose treatment period, blood sampling was conducted on day 1 at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, and 24 hours postdose; on days 2 and 3 at 2, 8, and 24 hours postdose; and on day 4 at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, 24, 36, 48, 60, and 72 hours ±5 minutes postdose. All 24-hour blood sample collections on days 1–3 were performed before administration of the next dose of the drug.

Bioanalytical assay

SDX was extracted from $100 \mu L$ of plasma using solid-phase extraction (SPE) with an Oasis HLB 96-well plate and SDX-d_6 as internal standard. The analysis was performed by liquid chromatography with positive ion electrospray tandem mass spectrometry (LC-MS/MS). Monitored mass transitions for SDX and SDX-d_6 were m/z $500.2 \rightarrow 142.1$ and m/z $506.2 \rightarrow 266.1$, respectively.

The main chromatographic conditions were as follows: Phenomenex Kinetex C18 $2.6 \mu m$, 50×2.1 mm high-performance LC column, 1 mM ammonium trifluoroacetate in water as aqueous mobile phase, acetonitrile/formic acid (1000:1) as organic phase, and gradient elution. Detection was performed with a Sciex API 5000 Triple Quad LC-MS/MS. The validation range of the method was 0.100–100 ng/mL with a lower limit of quantitation (LLOQ) of 0.100 ng/mL. The intra- and inter-run precision (coefficient of variance [CV]) was <7.4% and <6.2%, respectively. The intra- and inter-run accuracy was 96.4%–107.5% and 99.0%–102.8%, respectively.

SPE with an Oasis HLB 96-well plate and racemic d,l-MPH-d_3 as internal standard was used to extract d-MPH and l-MPH from $50 \mu L$ of plasma. The analysis was performed by LC-MS/MS. Monitored mass transitions for MPH and MPH-d_3 were m/z $234.3 \rightarrow 84.1$ and m/z $237.3 \rightarrow 84.1$, respectively.

The main chromatographic conditions were Supelco CHIR-OBIOTIC $5 \mu m$, 2.1×150 mm high-performance LC column, methanol/ethanol/ammonium trifluoroacetate (600:400:0.1, vol/vol/wt) as mobile phase, and isocratic elution. Detection was performed with a Sciex API 5000 Triple Quad LC-MS/MS. The validation range of the method was 0.200–200 ng/mL with an LLOQ of 0.200 ng/mL. The intra- and inter-run precision was <4.1% and <6.5%, respectively. The intra- and inter-run accuracy was 100.3%–117.1% and 94.7%–108.5%, respectively.

PK analysis

Plasma concentrations of SDX and d-MPH were determined after each treatment. Values obtained were used to derive the following PK parameters for SDX and d-MPH: maximum concentration in plasma (C_{max}), time to reach maximum concentration (T_{max}), terminal half-life ($T_{1/2}$), weight-normalized clearance (CL/F/W, with $W =$ body weight), weight-normalized volume of distribution (V_z/F/W), and areas under the concentration–time curve from time-zero to 24 hours postdose (AUC_{0-24h}), from time-zero to the time of the last quantifiable concentration (AUC_{0-last}), and time-zero extrapolated to infinity (AUC_{0-inf}). Concentration–time data for SDX and d-MPH in plasma were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3; Certara, Inc.).

TABLE 1. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Parameter	Statistic	All subjects (N = 24)
Age at screening (years)	Mean	37.2
	SD	10.0
	Median	36.0
	Range	20–53
Gender		
Male	N (%)	18 (75.0)
Female	N (%)	6 (25.0)
Race		
White	N (%)	11 (45.8)
Black or African American	N (%)	12 (50.0)
Asian	N (%)	1 (4.2)
Height at screening (cm)	Mean	173.27
	Median	172.75
	Range	162.0–186.9
Weight at screening (kg)	Mean	80.84
	Median	83.15
	Range	55.5–93.8
BMI at screening (kg/m^2)	Mean	26.95
	Median	27.35
	Range	19.9–30.8

BMI, body mass index; SD, standard deviation.

Statistical analysis

Parametric and nonparametric descriptive statistics were calculated for demographic characteristics (e.g., age, sex, race and ethnicity), baseline characteristics (e.g., body weight, height, body mass index), and each PK parameter. Parametric descriptive statistics included the number of subjects (n), arithmetic mean and standard deviation, percent coefficient of variation (%CV), and 95% confidence intervals (CI) around the mean. The PK parameters for each dose of SDX/d-MPH were normalized to the 39.2/7.8-mg dose by multiplying the values for the 26.1/5.2-mg dose by 1.5 and the values for the 52.3/10.4-mg dose by 0.75.
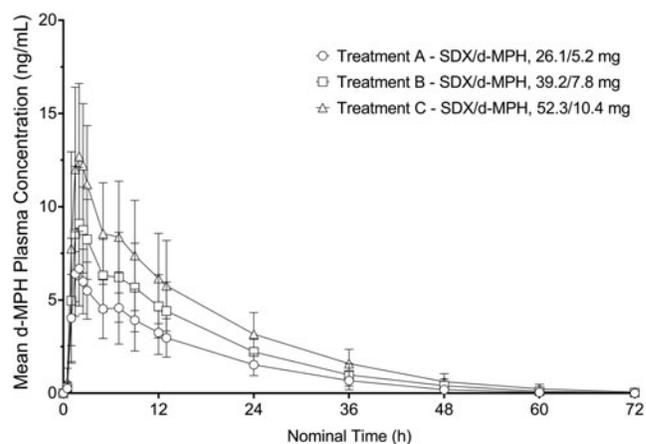

FIG. 1. Plasma concentration–time curve (mean ± standard deviation) for d-MPH after Treatments A, B, and C. Treatment A: SDX/d-MPH 26.1/5.2 mg; total equivalent d-MPH HCl, 20 mg. Treatment B: SDX/d-MPH 39.2/7.8 mg; total equivalent d-MPH HCl, 30 mg. Treatment C: SDX/d-MPH 52.3/10.4 mg; total equivalent d-MPH HCl, 40 mg. $n = 23$. d-MPH, dexmethylphenidate; SDX, serdexmethylphenidate.

TABLE 2. PLASMA PHARMACOKINETIC PARAMETERS FOR DEXMETHYLPHENIDATE AFTER SINGLE ORAL DOSE
ADMINISTRATION OF TREATMENTS A, B, AND C

	Treatment		
	A	B	C
C_{max} (ng/mL)	7.1 ± 2.1	9.8 ± 2.8	13.8 ± 3.8
T_{max} (hours)	2.0 (1.5–9.0)	2.0 (1.5–9.0)	2.0 (1.0–7.0)
$T_{1/2}$ (hours)	9.7 ± 3.3	10.3 ± 3.6	10.8 ± 3.0
$AUC_{0–last}$ (h*ng/mL)	97.2 ± 28.8	142.5 ± 41.2	199.8 ± 57.2
$AUC_{0–24h}$ (h*ng/mL)	79.2 ± 23.4	113.4 ± 32.8	153.2 ± 47.9
$AUC_{0–inf}$ (h*ng/mL)	102.4 ± 27.8	148.6 ± 40.9	206.0 ± 57.2
Clearance (CL/L/kg)	2.62 ± 0.83	2.71 ± 0.84	2.61 ± 0.80
Volume of distribution (V_z/F/kg)	38.89 ± 25.06	41.92 ± 24.61	41.93 ± 20.51

Parameters presented as mean ± SD with the exception of T_{max}, which is presented as median (range). Descriptive statistics for Treatments A, B, and C. Treatment A: SDX/d-MPH 26.1/5.2 mg; total equivalent d-MPH, 20 mg. Treatment B: SDX/d-MPH 39.2/7.8 mg; total equivalent d-MPH, 30 mg. Treatment C: SDX/d-MPH 52.3/10.4 mg; total equivalent d-MPH, 40 mg (n = 23).

$AUC_{0–24h}$, area under the concentration–time curve from time-zero to 24 hours postdose; $AUC_{0–last}$, AUC from time-zero to the time of the last quantifiable concentration; $AUC_{0–inf}$, AUC from time-zero extrapolated to infinity; C_{max}, maximum concentration in plasma; d-MPH, dexmethylphenidate; SD, standard of deviation; SDX, serdexmethylphenidate; T_{max}, time to reach maximum concentration; $T_{1/2}$, terminal half-life.

Differences in the dose-normalized PK parameters for d-MPH between the three treatments of the single-dose treatment period were analyzed using analysis of variance for a three-way crossover design. The model was applied to the natural log (ln)-transformed data with sequence, period, and treatment as the fixed effects and subject within sequence as a random effect. Treatment differences in T_{max} and $T_{1/2}$ for SDX and d-MPH were analyzed using the Wilcoxon signed rank nonparametric test.

Dose proportionality of C_{max}, $AUC_{0–last}$, $AUC_{0–24h}$, and $AUC_{0–inf}$ for d-MPH and SDX was assessed using a power analysis with mixed effects (Smith et al. 2000). The power model equation is $Y = \alpha \times (dose)^\beta$ where Y is the PK parameter evaluated, α is the expected value of Y for a reference dose, and β is the proportionality exponent. A mixed-effects model, allowing for random between-subject variability in α and β, was implemented to estimate the proportionality constant and its 90% CI. Dose proportionality was declared if the calculated 90% CI lay within the acceptance range $[1 + \log(\Theta_L)/\log(R), 1 + \log(\Theta_H)/\log(R)]$, where Θ_L and Θ_H are the lower and upper limits of the CI (0.8 and 1.25, respectively) and R is the ratio between the highest and lowest doses in the study ($R = 2$ in this study).

Statistical comparison of the d-MPH PK parameters of exposure (C_{max}, C_{min}, $AUC_{0–24h}$, $AUC_{0–3h}$, $AUC_{3–7h}$, and $AUC_{7–12h}$) between the first and last doses of the multiple-dose treatment phase was performed using analysis of variance on the ln-transformed data.

Results

Subjects and demographics

A total of 24 participants enrolled in the study, and 23 received the single-dose and multiple-dose treatments. One participant was withdrawn early after administration of Treatment B by the investigator, because of the adverse event (AE) ventricular extrasystoles. The AE was grade 1 in severity, considered possibly related to study medication, and resolved within 5 hours of onset.

TABLE 3. STATISTICAL ANALYSIS OF THE DOSE-NORMALIZED NATURAL LOG-TRANSFORMED SYSTEMIC EXPOSURE
OF DEXMETHYLPHENIDATE COMPARING SINGLE-DOSE ADMINISTRATION OF TREATMENTS A AND C VERSUS TREATMENT B

Test versus Ref	Dependent variable	GeoMean[a] test	GeoMean[a] Ref	Ratio (%)[b] (test/Ref)	90% CI lower	90% CI upper
A versus B	$\ln(C_{max})$	10.1338	9.4181	107.60	101.80	113.73
	$\ln(AUC_{0–24h})$	112.1968	107.4592	104.41	100.77	108.18
	$\ln(AUC_{0–last})$	138.3565	135.7108	101.95	98.40	105.63
	$\ln(AUC_{0–inf})$	147.0757	142.2095	103.42	100.13	106.82
C versus B	$\ln(C_{max})$	9.9278	9.4181	105.41	99.73	111.42
	$\ln(AUC_{0–24h})$	108.0530	107.4592	100.55	97.05	104.18
	$\ln(AUC_{0–last})$	142.9778	135.7108	105.35	101.69	109.15
	$\ln(AUC_{0–inf})$	147.9301	142.2095	104.02	100.71	107.44

Treatment A: SDX/d-MPH 26.1/5.2 mg; total equivalent d-MPH, 20 mg. Treatment B: SDX/d-MPH 39.2/7.8 mg; total equivalent d-MPH, 30 mg. Treatment C: SDX/d-MPH 52.3/10.4 mg; total equivalent d-MPH, 40 mg.
[a]Geometric mean based on least-squares mean of log-transformed parameter values.
[b]Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref).
$AUC_{0–24h}$, area under the concentration–time curve from time-zero to 24 hours postdose; $AUC_{0–last}$, AUC from time-zero to the time of the last quantifiable concentration; $AUC_{0–inf}$, AUC from time-zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum concentration in plasma; d-MPH, dexmethylphenidate; GeoMean, geometric mean; Ref, reference; SDX, serdexmethylphenidate; T_{max}, time to reach maximum concentration; $T_{1/2}$, terminal half-life.
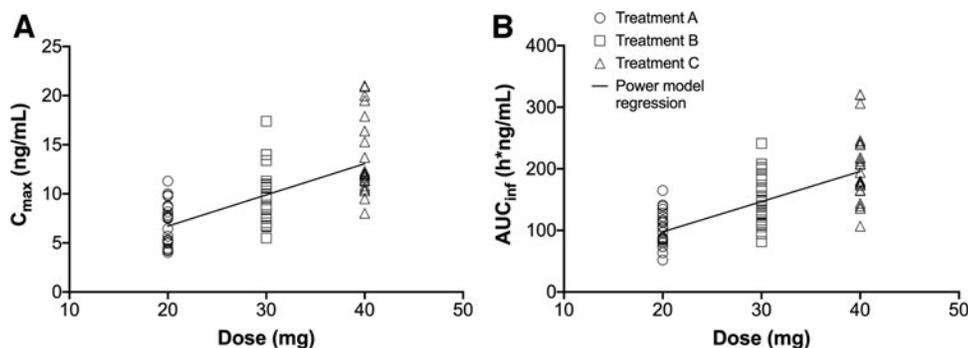
FIG. 2. Power model regression analysis of total equivalent d-MPH dose versus plasma d-MPH (**A**) C_{max} and (**B**) AUC_{0-inf}. (**A**) Intercept = −0.9812; slope = 0.9625. (**B**) Intercept = 1.5806; slope = 1.0021. Treatment A: SDX/d-MPH 26.1/5.2 mg; total equivalent d-MPH HCl, 20 mg. Treatment B: SDX/d-MPH 39.2/7.8 mg; total equivalent d-MPH HCl, 30 mg. Treatment C: SDX/d-MPH 52.3/10.4 mg; total equivalent d-MPH HCl, 40 mg. $n = 23$. AUC_{0-inf}, area under the concentration–time curve from time-zero extrapolated to infinity; C_{max}, maximum concentration in plasma; d-MPH, dexmethylphenidate; SDX, serdexmethylphenidate.

Table 1 shows the demographic and baseline characteristics of the intent-to-treat population. Median age of the participants was 36 years (range, 20–53 years), and most were men (75%).

PK properties of SDX/d-MPH in the single-dose study

The PK profile of SDX/d-MPH exhibited a single d-MPH concentration peak at about 2 hours postadministration, followed by a gradual elimination through the remainder of the 72-hour assessment period.

The following results represent mean ± standard deviation unless stated otherwise. After each single dose of SDX/d-MPH (26.1/5.2 mg, 9.2/7.8 mg, or 52.3/10.4 mg), d-MPH peak plasma concentrations were 7.1 ± 2.1, 9.8 ± 2.8, or 13.8 ± 3.8 ng/mL, respectively, followed by a gradual decline in concentration through the last time point (72 hours). The same doses yielded an AUC_{0-24h} of 79.2 ± 23.4, 113.4 ± 32.8, and 153.2 ± 47.9 h*ng/mL, respectively (Fig. 1; Table 2).

At 13 hours postdose, plasma d-MPH concentrations were 2.9 ± 1.0, 4.4 ± 1.5, and 5.7 ± 2.4 ng/mL after a single dose of SDX/d-MPH 26.1/5.2, 39.2/7.8, and 52.3/10.4 mg, respectively. Median d-MPH T_{max} occurred at 2.00 hours postdose for all

treatments, and median d-MPH $T_{1/2}$ values ranged from 8.59 to 10.54 hours, with no significant differences observed among the treatment groups (Table 2). Mean body weight-normalized clearance and volume-of-distribution values for d-MPH did not differ across the three treatments. Weight-normalized clearance values (CL/F/weight) for d-MPH ranged from 2.6 ± 0.8 L/[h·kg] (SDX/d-MPH 52.3/10.4 mg) to 2.7 ± 0.8 L/[h·kg] (SDX/d-MPH 39.2/7.8 mg), and weight-normalized volume-of-distribution values (V_z/F/weight) for d-MPH ranged from 38.8 ± 25.0 L/kg (SDX/d-MPH 26.1/5.2 mg) to 41.9 ± 20.5 L/kg (SDX/d-MPH 52.3/10.4 mg) (Table 2).

Dose-normalized mean maximum and total d-MPH exposure, as measured by C_{max}, AUC_{0-last}, and AUC_{0-inf}, were similar when comparing SDX/d-MPH 26.1/5.2 mg and SDX/d-MPH 52.3/10.4 mg with SDX/d-MPH 39.2/7.8 mg (Table 3).

Dose proportionality of PK parameters

After a single-dose administration of SDX/d-MPH 26.1/5.2, 39.2/7.8, and 52.3/10.4 mg, d-MPH C_{max} and AUC_{0-inf} values increased proportionally with the SDX/d-MPH dose (Fig. 2A, B; Supplementary Table S1). Dose proportionality of C_{max} and AUC_{0-inf}
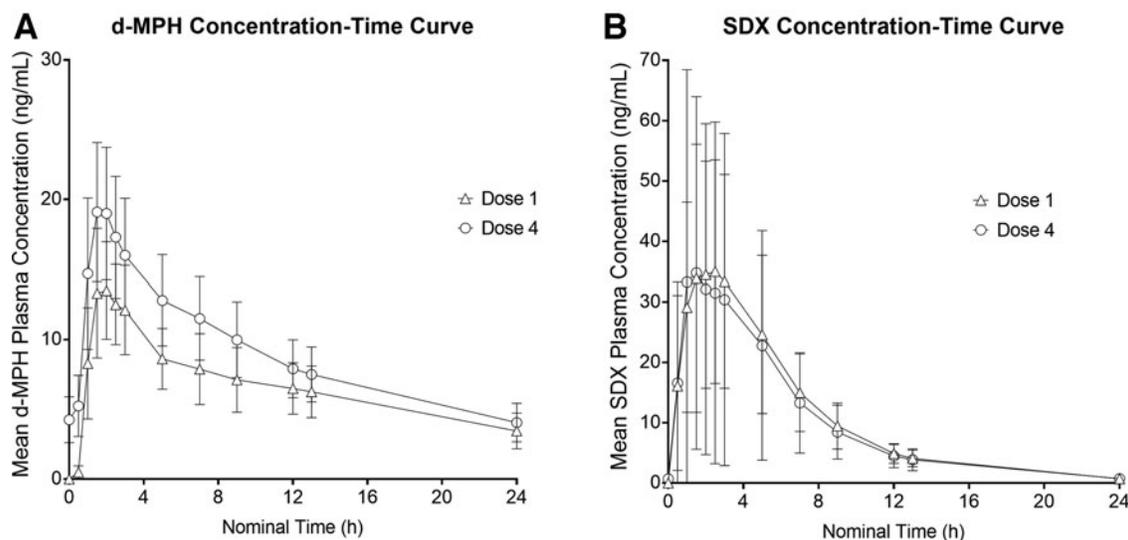
FIG. 3. Plasma concentration–time curve (mean ± standard deviation) for (**A**) d-MPH and (**B**) SDX after 1 and 4 doses of Treatment D: 52.3/10.4 mg SDX/d-MPH, 40 mg total equivalent d-MPH HCl. $n = 23$. d-MPH, dexmethylphenidate; SDX, serdexmethylphenidate.

TABLE 4. PLASMA PHARMACOKINETIC PARAMETERS FOR SERDEXMETHYLPHENIDATE AND DEXMETHYLPHENIDATE
AFTER MULTIPLE ORAL DOSE ADMINISTRATION OF TREATMENT D

	SDX		d-MPH	
	Day 1	Day 4	Day 1	Day 4
C_{max} (ng/mL)	41.8 ± 23.5	41.7 ± 38.0	14.9 ± 3.9	20.0 ± 4.7
T_{max} (h)	2.18 ± 1.0	1.8 ± 1.0	1.9 ± 0.5	1.8 ± 0.4
$T_{1/2}$ (h)	—	5.5 ± 1.7	—	9.8 ± 2.5
AUC_{0-24h} (h*ng/mL)	256.7 ± 108.5	241.2 ± 159.9	159.3 ± 38.3	215.4 ± 49.4
AUC_{0-last} (h*ng/mL)	—	246.9 ± 161.0	—	280.5 ± 69.8
AUC_{0-inf} (h*ng/mL)	—	248.6 ± 160.8	—	291.7 ± 69.1
Clearance (CL/L/Kg)	—	36.67 ± 1.633	—	2.44 ± 0.65
Volume of distribution (V_z/F/kg)	—	29.56 ± 16.40	—	33.88 ± 12.9
AR C_{max}	—	1.004 ± 0.5657	—	1.366 ± 0.2080
AR C_{min}	—	0.9705 ± 0.3011	—	1.152 ± 0.2658
AR AUC_{0-24h}	—	0.9196 ± 0.3016	—	1.365 ± 0.1516
AR k_{el}	—	1.060 ± 0.06282	—	1.231 ± 0.1203

Descriptive statistics of PK parameters for SDX and d-MPH after a single and multiple doses of Treatment D: SDX/d-MPH 52.3/10.4 mg; 40 mg total equivalent d-MPH HCl. ($n = 23$).

AR, accumulation ratio; AUC_{0-24h}, area under the concentration–time curve from time-zero to 24 hours postdose; AUC_{0-last}, AUC from time-zero to the time of the last quantifiable concentration; AUC_{0-inf}, AUC from time-zero extrapolated to infinity; C_{max}, maximum concentration in plasma; d-MPH, dexmethylphenidate; k_{el}, elimination rate constant; SDX, serdexmethylphenidate; T_{max}, time to reach maximum concentration; $T_{1/2}$, terminal half-life.

for d-MPH was formally evaluated using power model regression analysis. In the results of a power analysis, slopes (β) for the parameters were close to 1 (Supplementary Table S1). The acceptance interval for dose proportionality (see Methods) in this study is [0.6781, 1.3219]. The 90% CI of β for all exposure parameters were wholly contained within [0.6781, 1.3219], thus indicating dose proportionality across the tested dose range. In addition, an estimated maximal dose ratio, ρ_1, was calculated up to which d-MPH exposure can be assumed to be dose proportional under the same study conditions.

The results indicated a wide range of theoretical dose proportionality for SDX/d-MPH with respect to d-MPH exposure parameters ($\sim$6.5-fold [C_{max}] to 82.7-fold [AUC_{0-inf}]; Supplementary Table S1). Similar findings were observed for the overall exposure parameters AUC_{0-24} and AUC_{0-last}.

PK properties of SDX/d-MPH in the multiple-dose study

Dexmethylphenidate. Mean plasma concentrations of d-MPH were higher after multiple doses of SDX/d-MPH 52.3/10.4 mg than after a single dose of SDX/d-MPH 52.3/10.4 mg (Fig. 3A; Table 4). Mean maximum (C_{max}), minimum (C_{min}), and total (AUC_{0-24h}) d-MPH exposure after multiple doses of SDX/d-MPH 52.3/10.4 mg were $\sim$35%, 12%, and 36% higher, respectively, than after a single dose, indicative of modest accumulation of d-MPH. Mean d-MPH exposure from 0 to 3 hours (AUC_{0-3h}), 3 to 7 hours (AUC_{3-7h}), and 7 to 12 hours (AUC_{7-12h}) after multiple doses of SDX/d-MPH 52.3/10.4-mg was $\sim$59%, 43%, and 38% higher, respectively, than after a single-dose administration. Steady-state concentrations of d-MPH were reached before the administration of the third dose (Supplementary Table S2).

Serdexmethylphenidate. Mean SDX prodrug maximum concentrations (C_{max}) were similar after a single dose and multiple doses of SDX/d-MPH 52.3/10.4 mg (Fig. 3B; Table 4). Accumulation ratios for SDX prodrug C_{max}, C_{min}, AUC_{0-24h}, and elimination rate constant (k_{el}) were close to 1 (1.004, 0.9705, 0.9169, and 1.060, respectively), indicating no accumulation of SDX at the test dose during the multiple-dose regimen (Table 4).

SDX/d-MPH composite PK profile

A composite PK profile was constructed to show the individual contributions of SDX and d-MPH to the observed combined d-MPH plasma concentrations after oral administration of SDX/d-MPH. Figure 4 shows the PK profile for immediate-release d-MPH 10.4 mg, SDX 52.3 mg, and SDX/d-MPH 52.3/10.4 mg. Mean plasma concentrations contributed by a single-entity d-MPH 10.4-mg component was derived from data previously reported for immediate-release d-MPH (Midha et al. 2001). After administration of single-entity SDX 52.3 mg, exposure to d-MPH was negligible (<1 ng/mL) for the first 2–3 hours postdose. At $\sim$3 hours
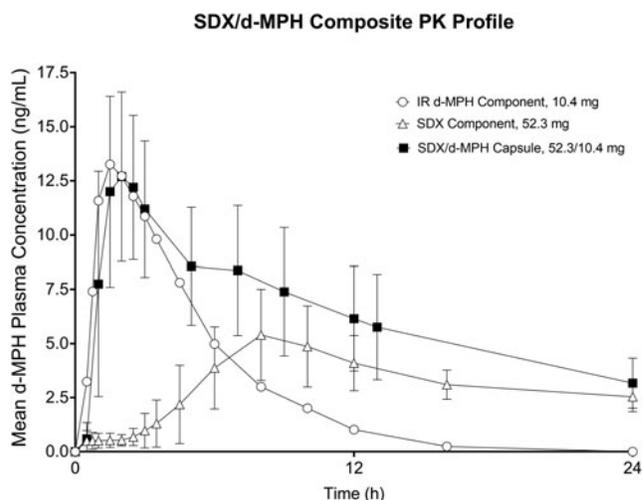
FIG. 4. Plasma concentration–time curve (mean ± standard deviation) for immediate-release d-MPH 10.4 mg, SDX 52.3 mg, and SDX/d-MPH 52.3/10.4 mg. The profile for IR d-MPH is included for comparison and was inferred from data reported in the summary basis of approval for d-MPH (Focalin®). Available from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-278_Focalin_medr_P1.pdf. IR, immediate-release; MPH, methylphenidate; SDX, serdexmethylphenidate.

TABLE 5. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS IN THE SAFETY POPULATION

	Treatment A (N=23)		Treatment B (N=24)		Treatment C (N=23)		Treatment D (N=23)		Overall (N=24)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n
TEAE	3 (13.0)	3	5 (20.8)	5	6 (26.1)	8	15 (65.2)	39	19 (79.2)	55
Related TEAE	2 (8.7)	2	5 (20.8)	5	5 (21.7)	7	14 (60.9)	37	17 (70.8)	51

Treatment A: SDX/d-MPH 26.1/5.2 mg; total equivalent d-MPH HCl, 20 mg. Treatment B: SDX/d-MPH 39.2/7.8 mg; total equivalent d-MPH HCl, 30 mg. Treatment C: SDX/d-MPH 52.3/10.4 mg; total equivalent d-MPH HCl, 40 mg.

d-MPH, dexmethylphenidate; SDX, serdexmethylphenidate; TEAE, treatment-emergent adverse event.

postdose, plasma d-MPH concentrations began to rise, with peak mean concentrations occurring at ~ 8 hours postdose before a gradual decline through 24 hours postdose. Mean d-MPH C_{max} and AUC_{0-last} for single-entity SDX 52.3 mg were 5.97 ± 2.04 ng/mL and 107.0 ± 20.21 h*ng/mL, respectively. Mean T_{max} and $T_{1/2}$ were 10.29 and 21.78 ± 9.82 hours, respectively.

After combined administration of these two compounds as SDX/d-MPH 52.3/10.4 mg, early exposure to d-MPH is governed primarily by the immediate-release d-MPH component, whereas midday to late-day exposure is governed by the gradual conversion of the SDX component to d-MPH. A noteworthy feature of the SDX/d-MPH PK curve is the slow d-MPH terminal elimination phase, resulting in a $T_{1/2}$ of 10.8 ± 3.0 hours.

Safety

Treatment-emergent AEs were reported in 19 participants (79.2%; Table 5). All AEs were grade 1 in severity, except one AE of rhinorrhea that was considered grade 2. There were no unexpected AEs related to the treatment. No serious AEs or clinically significant abnormalities in physical examinations were reported. One participant discontinued because of an AE. There were no deaths during the trial. The most frequent AEs were dry mouth with 5 reported cases (1 case reported by 1 participant [4.3%] after Treatment C and 4 by 2 participants [8.7%] after Treatment D), somnolence with 4 reported cases (1 case reported by 1 participant [4.3%] after Treatment C and 3 reported by 2 participants [8.7%] after Treatment D), and tachycardia with 4 reported cases (all 4 reported by 3 participants [13.0%] after Treatment D).

Discussion

The present study describes the dose proportionality and steady-state PK characteristics of SDX/d-MPH, a novel prodrug combination containing a molar ratio of 70% SDX and 30% d-MPH, now approved in the United States for the treatment of ADHD (Azstarys™). Administration of 26.1/5.2, 39.2/7.8, and 52.3/10.4 mg of SDX/d-MPH resulted in a single d-MPH plasma concentration peak ~ 2 hours postdose, followed by a gradual elimination phase, resulting in a long half-life of 10.8 hours. Appreciable plasma concentrations of d-MPH were still observed 13 hours after single-dose administration of all three doses of SDX/d-MPH. In the current study, low to moderate accumulation of d-MPH, but none of SDX, was observed after administration of multiple consecutive doses of SDX/d-MPH. The long half-life of d-MPH imparted by SDX/d-MPH and the resulting gradual decrease of plasma concentrations may slow the loss-of-treatment effect in the evening hours.

To achieve late-day efficacy, some extended-duration products incorporate a second MPH peak, potentially increasing the likelihood of AEs later in the day, either from high exposure levels during the second peak or from a precipitous drop in exposure following the second peak. These symptoms can be severe enough to lead to treatment discontinuation in some patients. The PK profile of SDX/d-MPH, which consists of a single peak and shallower decline in d-MPH plasma concentrations, may promote a more consistent drug effect throughout the day.

Determining the predictability of d-MPH exposure across the clinical dose range is important for appropriate titration in patients. Accordingly, in the present study, a power model regression analysis showed C_{max} and AUC_{0-inf} to be dose proportional at all dosage strengths, indicating predictable exposure and the opportunity for initial dose titration and ongoing dose adjustments.

Children receiving ADHD medications may experience uncontrolled symptoms in the early morning and the early evening hours, resulting in an increased burden for children and their parents (Whalen et al. 2006; Sallee 2015). Data from the present study suggest that the PK characteristics of SDX/d-MPH may offer more desirable symptom management from early morning through early evening. Specifically, the long half-life of d-MPH may delay loss of efficacy near the end of the day without the need for additional or higher doses, and attenuate potential rebound effects that may be engendered by faster elimination of d-MPH. In addition, the SDX/d-MPH PK attributes reported in the current study are consistent with the efficacy–time profile determined in a separate trial in children 6–12 years of age with ADHD who were treated with daily doses of SDX/d-MPH (Kollins et al. 2021).

Conclusions

The new treatment containing a coformulation of SDX/d-MPH exhibits a single d-MPH plasma concentration peak ~ 2 hours after administration, followed by a gradual elimination phase defined by a long half-life of 10.8 hours. The immediate-release d-MPH component accounts for the rapid increase in plasma d-MPH concentrations, while the SDX component provides sustained plasma d-MPH concentrations through the evening hours. SDX/d-MPH also exhibited dose proportionality across the dose range studied, thus providing predictable increases in d-MPH exposure during dose titration or when making later dose adjustments. Upon repeat dosing of SDX/d-MPH, there was low to modest accumulation of d-MPH but not the intact prodrug, SDX. Steady-state plasma concentrations were achieved before the third dose.

Together, these data indicate that SDX/d-MPH may offer a novel treatment capable of addressing current unmet needs for patients with ADHD as they relate to symptom control during waking hours.

Clinical Significance

Current d-MPH–based treatments leave unmet needs for some patients with ADHD and their families. The present study

demonstrated key PK characteristics of a novel prodrug coformulated with d-MPH that may address some of these unmet needs, namely, a rapid onset of d-MPH exposure followed by a very gradual decline until the next dose. This PK profile can potentially treat ADHD symptoms consistently from early morning through early evening. Individual patient titration and potential subsequent dose changes are facilitated by consistent and predictable exposure across the available dose range.

Disclosures

All authors were responsible for the study design, data analysis, and interpretation and provided critical review and editing of all drafts of the article. R.B., A.B., T.C.M., S.G., and A.S. are employees and shareholders of KemPharm, Inc. C.O. is an employee and shareholder of Corium, Inc.

Supplementary Material

Supplementary Data S1

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