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Single- and Multiple-Dose Pharmacokinetics of an Oral Mixed Amphetamine Salts Extended-Release Formulation in Adults

By Susan B. Clausen, PhD, Stephanie C. Read, MS, and Simon J. Tulloch, MD

FOCUS POINTS

- Psychostimulant medications are well tolerated and are considered first-line medications for reducing the core symptoms of attention-deficit/hyperactivity disorder.
- Two studies described here assessed single- and multiple-dose pharmacokinetics of mixed amphetamine salts extended release (MAS XR) in healthy adults.
- Following a single oral dose of MAS XR (20, 40, or 60 mg), a 3:1 ratio of dextroamphetamine (D-amphetamine) to levoamphetamine (L-amphetamine) was observed for $AUC_{0-\infty}$ and C_{max}. Time to maximum observed drug concentration (T_{max}) was ~5 hours for each isomer, and plasma concentrations and extent of exposure for D-amphetamine and L-amphetamine were dose proportional.
- Following multiple-dose administration of MAS XR 30 mg/day, a 3:1 ratio of D-amphetamine to L-amphetamine was observed for $AUC_{0-\infty}$ and C_{max}; T_{max} was just over 4 hours for each isomer.
- The concentrations of D-and L-amphetamine rise rapidly after single- and multiple-dose administration due to the immediate-release component in MAS XR. T_{max} occurs at ~5 hours. Drug concentrations decrease slowly between 5 and 12 hours, likely reflecting the continuing absorption of delayed-release MAS XR pellets during this time.

ABSTRACT

Objectives: *Assess the bioavailability of mixed amphetamine salts extended-release (MAS XR) 30-mg capsules and the dose proportionality of pharmacokinetic measures for MAS XR 20, 40, and 60 mg.*

Methods: *Study A, an open-label single-period study, and Study B, a randomized, open-label, three-way crossover study, were conducted in healthy adults in a clinical research unit. In Study A, 20 subjects received a single MAS XR 30-mg capsule by mouth daily for 7 days. In Study B, 12 subjects received single oral doses of MAS XR 20, 40, and 60 mg separated by 7–14-day washout periods.*

Findings: *Plasma dextroamphetamine (D-amphetamine) and levoamphetamine (L-amphetamine) concentrations were measured using a validated LC-MS/MS method. In Study A, a 3:1 ratio of D-amphetamine to L-amphetamine was observed for $AUC_{0-\infty}$ and C_{max}. T_{max} was 4.2 and 4.3 hours for D-amphetamine to L-amphetamine, respectively. In Study B, for D- and L-amphetamine, statistically significant differences were observed for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} between all doses; there was a linear relationship between pharmacokinetic variables and dose and T_{max} was similar for each isomer (range: 4.5–5.3 hours) with all given MAS XR doses.*

Conclusion: *The extent of exposure as assessed by mean AUC_{0-24} and C_{max} reflected the 3:1 ratio of D-amphetamine to L-amphetamine in MAS XR 30-mg capsules. The pharmacokinetic profiles of MAS XR 20, 40, and 60 mg are dose proportional for the isomers.*

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder that is one of the most prevalent chronic health conditions in children, affecting 2% to 18% of school-age youth in the United States.[1] Although ADHD traditionally has been considered a pediatric disorder, up to 65% of children with a diagnosis of ADHD will continue to display behavioral problems and symptoms of the disorder into their adult lives.[2] Epidemiologic

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data indicate that the prevalence of adult ADHD according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria is ~5%.[3,4] Given an adult population of 209 million in the US, a 5% prevalence rate suggests that as many as 10 million adults may be affected by ADHD.[5] The core symptoms of ADHD—inattention, impulsivity, and hyperactivity—are apparent in adults with ADHD, although hyperactive symptoms diminish with age.[6] As in children with ADHD, adults show functional impairments in multiple domains, often including poor educational performance, occupational problems, and relationship difficulties.

Psychostimulant medications are well tolerated and are considered first-line medication for reducing the core symptoms of ADHD.[7-9] Although the specific mechanism of action has not been fully elucidated, stimulants both accentuate the release from and block the reuptake of the neurotransmitters dopamine and norepinephrine into presynaptic neurons.[10] The pharmacokinetic and pharmacodynamic effects of amphetamine have been described in adults and children.[11-14] The absorption of amphetamine is rapid and complete from the gastrointestinal tract, and maximum plasma concentrations are reached in 3–4 hours. Clinical behavioral effects are most apparent during the absorption phase and decrease after peak plasma concentrations are reached.[11-14]

Immediate-release mixed amphetamine salts (MAS IR) is a formulation of neutral salts of D-amphetamine sulfate, amphetamine sulfate, D-amphetamine saccharate, and amphetamine aspartate. For each MAS IR tablet, the combination of salts and D- and L-isomers results in a 3:1 ratio of D-amphetamine to L-amphetamine. The efficacy and tolerability of MAS IR in the treatment of children and adults with ADHD have been demonstrated in clinical studies.[15-24]

The short duration of action of most stimulant medications has necessitated multiple daily dosing to provide effective symptom management for many children.[25,26] The complexity and inconvenience of multiple daily-dose stimulant regimens can be problematic for a chronic disorder such as ADHD, and noncompliance has been well documented.[27,28] Children and adults will benefit from the recent development of long-acting amphetamine formulations, which eliminate the need for multiple daily doses. The availability of once-daily dosage formulations for ADHD patients facilitates increased convenience and compliance, and is likely to increase treatment effectiveness and satisfaction.[29]

Mixed amphetamine salts extended-release (MAS XR) capsules contain the same 3:1 ratio of D-amphetamine to L-amphetamine present in MAS IR tablets. MAS XR is formulated for once-daily dosing via the inclusion of both immediate-release beads, which release the first half of the dose upon ingestion, and delayed-release beads, which begin to release the second half of the dose 4 hours later. The bioavailability and pharmacokinetic profiles observed for both D- and L-amphetamine after once-daily dosing of MAS XR 20 mg are comparable with those observed after twice-daily dosing of MAS IR 10 mg with a 4-hour interval.[30] Because the immediate- and delayed-release beads are distributed in a 50:50 ratio uniformly throughout the capsule, MAS XR capsules can be opened and sprinkled on food without affecting bioavailability.[30] Food has little effect on plasma amphetamine levels, although gastrointestinal acidifying agents (eg, ascorbic acid) may decrease bioavailability by reducing absorption.

The efficacy, safety, and extended duration of action of MAS XR 10-, 20-, and 30-mg capsules were demonstrated in two randomized, double-blind, placebo-controlled studies of children with ADHD: one conducted in an analog classroom setting, and the other in a naturalistic home and school environment.[31,32] The long-term effectiveness and tolerability of MAS XR have been demonstrated in a 2-year study.[33] In addition, a well-controlled study of MAS XR 20, 40, and 60 mg once daily in adults with ADHD demonstrated significant symptom improvement and 12-hour duration of action in this population, and long-term results show sustained effectiveness.[34,35]

Detailed pharmacokinetic studies of MAS XR have been limited primarily to the pediatric population[33] and as such may not generalize to the adult ADHD population. Earlier studies of amphetamine agents suggest, for instance, that the elimination half-life of both D- and L-amphetamine may be relatively longer (by ~1–2 hours) in adults than in children.[13,14] This raises the possibility for potential differences in the pharmacokinetic profile of MAS XR in adults relative to what has already been well described in children. To better characterize the pharmacokinetic profile of MAS XR in adults and to facilitate development of MAS XR as a first-line treatment for adults with ADHD, two separate studies in healthy adult volunteers using doses up to 60 mg/day were conducted. The objective of the first study was to assess the steady-state bioavailability of D- and L-amphetamine after oral dosing of MAS XR 30 mg

in healthy adults. The objective of the second study was to assess the dose proportionality of D- and L-amphetamine after single oral doses of MAS XR 20, 40, and 60 mg in healthy adults.

METHODS

Subjects

Men and women between 19 and 55 years of age with no clinically significant abnormal findings on physical examination, medical history, or clinical laboratory results during screening were admitted to the studies. Body weight was not more than 10% below or 20% above ideal weight for height and estimated frame adapted from the 1983 Metropolitan Life Insurance Tables.

Major exclusion criteria were treatment with any known cytochrome P450 enzyme-altering agents (eg, barbiturates, phenothiazines, cimetidine) within 30 days before or during the study; use of any other prescription medicine within 14 days before or during the study (excluding hormonal contraceptive or hormonal replacement therapy for women); use of any over-the-counter agent within 7 days before or during the study; history of allergic or adverse response to amphetamine or any related drug; positive urine screen for alcohol or drugs of abuse or a history of drug or alcohol abuse; pregnancy or lactation; history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease; or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or affect the validity of the study results.

Subjects were prohibited from ingesting food or beverages containing alcohol, caffeine, or any xanthine-containing product 48 hours before and during each period of confinement; from ingesting fruit or juices (including grapefruit) containing ascorbic acid during confinement; and from participating in strenuous exercise during confinement.

All subjects gave written, informed consent, and the studies were approved by the institutional review boards of MDS Harris, Phoenix, AZ (Study A), and MDS Harris, Lincoln, NE (Study B). Shire Pharmaceuticals Inc. supplied all study drugs.

Study A Design

Study A was an open-label, single-period, multiple-dose study in 20 healthy subjects. Each subject received a total of seven doses, administered as single MAS XR 30-mg capsules on seven consecutive mornings. The seventh (final) dose was administered after a 10-hour overnight fast.

A 30-mg dose was selected to enable quantitation of anticipated blood levels of both D- and L-amphetamine over the 60-hour time period. Furthermore, 30 mg is the highest dosage strength marketed for MAS XR capsules, and previous experience suggested that this dose would be well tolerated by healthy subjects.

Drug Administration

Subjects were admitted to the clinic in the evening, at least 10 hours before the first scheduled dose. At check-in, subjects completed a brief written questionnaire to affirm that exclusion criteria and restrictions had not been violated since the screening period. A urine sample was collected to test for alcohol and drugs of abuse, and a blood sample was collected from women for a serum pregnancy test. Subjects remained at the clinic until completion of the 36-hour postdose blood collection on day 8 and returned to the clinic for the 48- and 60-hour postdose specimen collections.

After check-in, each subject received a meal or an evening snack, and water was allowed ad libitum. On days 1 through 6, subjects received clinic meals of breakfast, lunch, dinner, and an evening snack according to a standard schedule and menu. All subjects observed a supervised fast for at least 10 hours before dosing on day 7. Water was allowed ad libitum during this time, except for 1 hour before and 1 hour after dosing on day 7. For 4 hours after drug administration on day 7, subjects were required to continue fasting and to remain in an upright position (sitting or standing) to assure proper stomach emptying. The standard meal schedule was resumed with lunch on day 7. On day 8, water was allowed ad libitum, and all subjects received clinic meals of breakfast, lunch, and dinner according to the standard schedule. Each daily dose was administered with 8 fl oz room-temperature tap water; a mouth check was performed after dosing to ensure that the capsule was swallowed.

Blood Collection

A total of 24 blood samples (7 mL per sample) were collected for determination of D- and L-amphetamine plasma levels. On days 1, 5, and 6, only predose blood samples were collected. On day 7 (steady state), blood samples were collected 5 minutes before dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours. At the screening visit, 15 mL of blood was collected for clinical laboratory evaluations; for women, an additional 5 mL was collected to test for pregnancy.

Blood samples were collected by venipuncture into tubes containing ethylenediaminetetraacetic acid (EDTA) and stored on ice before plasma was separated by centrifugation (~2,500 rpm x 15 minutes at 4°C). All plasma samples were frozen and stored at -20°C until assay was performed.

Safety Evaluations

Adverse event data were obtained by observation and unsolicited reporting throughout the study. A 12-lead electrocardiogram (ECG) was obtained, and sitting vital signs (blood pressure and pulse) were measured at screening and each morning before dosing.

Statistical Analysis

The pharmacokinetic variables for D- and L-amphetamine were tabulated using descriptive statistics (N, mean, standard deviation, median, and minimum and maximum values) for all subjects with evaluative data. Adverse events, blood pressure, and pulse were tabulated descriptively. There were no statistical comparisons of adverse events; vital signs were compared using a paired *t* test. All statistical analyses (for both studies) were performed using SAS statistical software, version 6.12 (SAS Institute, Cary, NC).

Study B Design

Study B was an open-label, three-way crossover study designed to assess the dose proportionality of MAS XR following single 20-, 40-, and 60-mg doses. A standard 3 x 3 Latin square was used to assign the 12 subjects to treatment sequences, with four subjects per sequence. In each sequence, subjects received a single dose of MAS XR 20 mg (2 x 10-mg capsules), 40 mg (2 x 20-mg capsules), or 60 mg (2 x 30-mg capsules) after an overnight fast. Subjects received the other treatments during subsequent study periods according to the randomization scheme. A washout period of 7 days separated each study period.

Drug Administration

Subjects were admitted to the clinic in the evening, at least 12 hours before the scheduled dose. At each treatment period check-in, subjects completed a brief written questionnaire to affirm that exclusion criteria and restrictions had not been violated since the screening or previous study period. A urine sample was collected to test for alcohol and drugs of abuse, and a blood sample was collected from women for a serum pregnancy test. Subjects remained at the clinic until completion of the 24-hour postdose blood collection and returned to the clinic for the 36-, 48-, and 60-hour postdose collections. After check-in, each subject received a standard evening meal ~12 hours before drug administration. Intact capsules were administered and a mouth check was performed after dosing to ensure that capsules were swallowed. Water was allowed ad libitum during the study, except for 1 hour before and 1 hour after dosing. For 4 hours after drug administration, subjects were required to continue fasting and to remain in an upright position (sitting or standing) to assure proper stomach emptying. A standard meal schedule resumed with lunch, dinner, and an evening snack for all subjects. This schedule of events was followed for each of the three treatment periods.

Blood Collection

A total of 57 blood samples per subject (7 mL per sample) were collected for determination of plasma D- and L-amphetamine levels. Beginning on each dosing day, 19 blood samples were collected from each subject through the 60-hour postdose interval during each study period. Blood samples were collected 5 minutes before dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, and 60 hours. Two additional blood samples were collected for the clinical laboratory evaluation at the screening visit. For women, another 25 mL was collected at each check-in period for a serum pregnancy test. Samples were collected by venipuncture into tubes containing EDTA and stored on ice before plasma was separated by centrifugation (~3,000 rpm × 10 minutes at 4°C). All plasma samples were stored at -20°C until analysis was performed.

Safety Evaluations

Adverse event data were obtained by the use of nondirected questioning at preselected times in addition to spontaneous reports throughout the study. Vital signs (sitting blood pressure and pulse) were measured at screening and at five other times at every dosing period (immediately before dosing and at 2, 4, 24, and 60 hours postdose).

Statistical Analysis

Descriptive statistics of D- and L-amphetamine were calculated for all pharmacokinetic variables for all subjects with evaluative data. An analysis of variance (ANOVA) model for a three-way crossover design with a general linear approach was applied to area under the curve (AUC), maximum observed drug concentration (C_{max}), time to maximum observed drug concentration (T_{max}), and elimination half-life ($t_{½}$) to determine differences between the doses. The model included sequence, subject within sequence, period, and dose. Profile analysis was performed to test the differences in the least-square estimated means between each pair of

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