Pharmacokinetics of a New Amphetamine Extended-Release Oral Liquid Suspension Under Fasted and Fed Conditions in Healthy Adults: A Randomized, Open-Label, Single-Dose, 3-Treatment Study

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ABSTRACT

Purpose: A new amphetamine extended-release liquid formulation (AMP XR-OS), intended for the treatment of attention-deficit/hyperactivity disorder, has been developed. This study was performed to determine if administration with food affected the rate of absorption or bioavailability of AMP XR-OS. The formulation was also compared with an equivalent dose of an extended-release mixed amphetamine salts reference product (30 mg) under fed conditions.

Methods: Thirty adult volunteers participated in this single-dose, open-label, randomized, 3-period, 3-treatment crossover study. Each participant received a single 15-mL dose of AMP XR-OS (equivalent to 30 mg of the reference drug) under fasted conditions, a single 15-mL dose of AMP XR-OS under fed conditions, and a single dose of the reference drug under fed conditions. A 7-day washout separated the 3 treatment periods. Blood samples were collected at predetermined time points and analyzed for *d*- and *l*-amphetamine. Pharmacokinetic parameters reported are $AUC_{0–5}$, $AUC_{0–last}$, $AUC_{5–last}$, and $AUC_{0–\infty}$; C_{max}; elimination $t_{1/2}$; and T_{max}. The geometric mean ratios and 90% CIs of C_{max}, $AUC_{0–last}$, and $AUC_{0–\infty}$were determined for the comparison of AMP XR-OS fed and fasted, and C_{max}, $AUC_{0–5}$, $AUC_{5–last}$, and $AUC_{0–\infty}$ were calculated for AMP XR-OS compared with the reference drug under fed conditions. Safety was also assessed.

Findings: Twenty-nine subjects completed the study. Subjects were mostly male, white, and of Hispanic/Latino ethnicity with a mean age of 35.83 years and a mean BMI of 25.36 kg/m^2. The 90% CIs of C_{max}, $AUC_{0–last}$, and $AUC_{0–\infty}$ for AMP XR-OS fasted versus fed were within the accepted 80% to 125% range, indicating lack of a food effect. In the comparison of AMP XR-OS fed versus the reference product, C_{max}, $AUC_{5–last}$, and $AUC_{0–\infty}$ were within the range to establish bioequivalence; however, $AUC_{0–5}$ was significantly higher for AMP XR-OS compared with that of the reference drug. This difference between products was likely due to the known delay of T_{max} and decreased exposure when the extended-release mixed amphetamine salts reference product is administered with food. A total of 36 mild or moderate adverse events were reported; 1 subject withdrew due to an adverse event, and no deaths occurred. These adverse events were consistent with the known pharmacodynamic effects of amphetamine.

Implications: The absence of a food effect may allow for AMP XR-OS to be administered with or without a meal. (*Clin Ther*. 2017;∎:∎∎∎–∎∎∎)

Key words: ADHD, amphetamine, drug delivery, food effect, pharmacokinetics, psychiatry.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and/or impulsivity that impair an individual's development and daily functioning.[1] Recent studies estimate a US prevalence of ~8% to 11% in children 4 to 17 years of

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age and, using the latest diagnostic criteria, 8% in adults.[2,3] Psychostimulant medications, including amphetamines, are effective in treating symptoms,[4–7] improving overall quality of life,[8,9] and reducing the morbidity associated with ADHD.[10] Thus, management guidelines recommend psychostimulant medication as a first-line pharmacologic option.[11]

Poor medication adherence is a concern with ADHD treatment, and the causes are multifactorial, including physical and lifestyle issues.[12] Once-daily extended-release psychostimulant formulations can increase rates of adherence compared with short-acting formulations, which require >1 dose to be administered during the day.[13] Difficulty swallowing also contributes to medication noncompliance. A 2016 US survey found that ~13% of pediatric patients and 13% of adult patients had trouble swallowing their ADHD medication; of these, 60% struggled to comply with the daily treatment regimen, and 40% discontinued their ADHD medication.[14] Alternative delivery formulations, such as liquids, chewable tablets, or orally disintegrating tablets, may be easier to swallow and more convenient for these patients than pills and capsules.

Clinical trials for a new once-daily extended-release amphetamine oral suspension formulation (AMP XR-OS) were recently completed. AMP XR-OS combines *d*- and *l*-amphetamine in a 3:1 ratio, and it is a nearly equivalent mixture of immediate-release and delayed-release particles.[15] The delayed-release properties are derived from a pH-dependent, acid-resistant coating that dissolves in the alkaline environment of the intestinal tract.

The presence of food can alter the pharmacokinetics (PK) of an orally administered drug.[16] For instance, guanfacine extended-release tablets (a nonstimulant ADHD medication) should not be taken with a high-fat meal because total exposure is significantly increased (~75% increase in C_{max} and 40% increase in exposure [AUC]).[17] ADHD stimulant medications may also be affected by food. Extended-release methylphenidate capsules* should be administered before a meal because food delays absorption and increases exposure (an average of 30% increase in C_{max} and 17% increase in AUC).[18] The present study assessed the effect of a standard US Food and Drug Administration (FDA) breakfast on the bioavailability of amphetamine after administration of AMP XR-OS to healthy adult volunteers.

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SUBJECTS AND METHODS

Study Design and Treatments

This was a single-dose, open-label, randomized, 3-period, 3-treatment crossover study. The protocol and related documents were approved by the IntegReview Ethical Review Board (Austin, Texas), and the study was performed in accordance with the guidelines established by the US Investigational New Drug regulations (US 21 CFR parts 50, 56, and 312), the Declaration of Helsinki and its amendments, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. All participants gave written informed consent before any study-specific evaluations were performed.

Thirty healthy adult participants were enrolled. The sample size was calculated using a power of 80%, a type I error of 5%, and accounting for dropouts. Participants received a single dose of AMP XR-OS under fasted conditions, a single dose of AMP XR-OS under fed conditions, and a single dose of an extended-release mixed amphetamine salts (MAS ER)† reference product under fed conditions. The study used a randomization schedule prepared by Worldwide Clinical Trials Early Phase Services, LLC (San Antonio, Texas). The MAS ER dose consisted of a 30-mg capsule administered orally with 60 mL of water. The 15-mL AMP XR-OS dose was administered orally without water and delivered amphetamine equivalent to 30-mg mixed amphetamine salts.

Participants in all 3 treatment conditions fasted overnight for at least 10 hours, and each administration was separated by a washout period of at least 7 days. Participants fasted for 4 hours after each treatment administration. The fed groups were dosed 5 minutes after consuming an FDA standard high-calorie, high-fat breakfast meal with a total of 30 minutes between the start of the meal and dosing. The breakfast was ~800 to 1000 calories, with 50% to 75% of the total calories from fat, 25% to 30% from carbohydrates, and the rest from protein.[16] The fasted group continued to fast until the time that they underwent dosing. For the initial 4 hours postdose, participants were not allowed to lie down and were instructed to remain seated unless otherwise directed.

†Trademark: Adderall XR® (Shire, Inc, Lexington, Massachusetts).