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A Population Pharmacokinetic Analysis of Dextroamphetamine in the Plasma and Hair of Healthy Adults

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Abstract

Background and Objective—Hair is an attractive matrix for amphetamine drug testing; however, little is known about the rate at which amphetamines are deposited into hair. Therefore, the purpose of this study was to determine the pharmacokinetics of oral dextroamphetamine in plasma and quantify the rate of deposition into hair in healthy adults using a linked population pharmacokinetic model.

Methods—Healthy adults >18 years of age received dextroamphetamine 10 mg orally for 7 days. Plasma samples were collected over 48 h following the final dose, and hair was collected 5 weeks following the first dose. NONMEM 7.2 was used to estimate dextroamphetamine oral absorption rate constant, apparent clearance and volume of distribution of the plasma compartment, the

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Author contributions Jessica K. Roberts performed the pharmacokinetic modeling and analysis, and drafted the manuscript; Sarah F. Cook advised the pharmacokinetic modeling, produced the model plots, and critically reviewed the manuscript; Chris Stockmann advised the pharmacokinetic modeling and critically reviewed the manuscript; Douglas E. Rollins (principal investigator) wrote the original study design, conducted the clinical study, and critically reviewed the manuscript; Diana G. Wilkins (principal investigator) wrote the original study design, conducted the clinical study, and critically reviewed the manuscript; and Catherine M. T. Sherwin advised the pharmacokinetic modeling, and critically reviewed the manuscript.

Compliance with Ethical Standards

Conflicts of interest Jessica K. Roberts, Sarah F. Cook, Chris Stockmann, Douglas E. Rollins, Diana G. Wilkins, and Catherine M. T. Sherwin have no financial relationships with any organisations that might have an interest in the submitted work, nor are there any other relationships or activities that could appear to have influenced the submitted work.

Ethical approval All procedures in this study were in accordance with the 1964 Helsinki declaration (and its amendments). This study was approved by the Institution Review Board at the University of Utah.

Informed consent All subjects were consented before their enrollment into the study.

plasma to hair incorporation rate constant, and the apparent volume of distribution in the hair compartment.

Results—Dextroamphetamine pharmacokinetics were well-described by a one-compartment model with combined additive and proportional error for the plasma compartment, which was linked to a single compartment for the hair. Apparent clearance and volume of distribution in the plasma compartment were scaled by current body weight (centered on the mean). Melanin hair concentration was included as a significant covariate on the hair compartment. Absorption rate constant, clearance, and volume of distribution for the plasma compartment were estimated as 0.527 h^{-1} (95 % CI 0.467–0.586), 28.7 L/h (95 % CI 27.1–30.3), and 377 L (95 % CI 326–428), respectively. The incorporation rate constant from plasma to hair was $1.60\text{e}^{-6} \text{ h}^{-1}$ (95 % CI 1.06e^{-6} – 2.14e^{-6}) and apparent volume of distribution in hair was 17.7 mg (95 % CI 12.5–22.8).

Conclusions—A one-compartment plasma model linked to a single compartment for hair successfully described the pharmacokinetics of dextroamphetamine in healthy adults. The volume of distribution and clearance of dextroamphetamine increased with weight, and the volume of distribution of the hair compartment increased with greater melanin concentrations.

1 Introduction

Hair is an attractive matrix for drug testing, especially for drugs of abuse of long-term use. It provides a non-invasive alternative to blood sampling and precludes the privacy concerns associated with urine testing. However, previous research has shown that hair pigmentation (melanin concentration) affects the extent and rate of drug incorporation into hair [1–4]. Basic drugs, such as amphetamine, codeine, nicotine, phencyclidine, and stanozolol have all been shown to have higher concentrations in darker hair (higher melanin concentrations) compared with lighter hair [1–3, 5–9]. In contrast, hair concentrations of phenobarbital and *N*-acetylamphetamine, which are acidic or neutral at physiological pH, have not been correlated with melanin concentrations [1, 5]. Mechanistic studies suggest that the positive charge of basic drugs at physiologic pH forms an ionic bond and/or Van der Waals interactions with negatively charged melanin polymers [10, 11]. This suggests that melanin concentration is an important factor when determining drug threshold concentrations permitted in hair for basic drugs at physiological pH.

Methamphetamine, which is also a basic drug, is a common drug of abuse that produces feelings of euphoria, increased sexuality, decreased anxiety, and increased energy [12]. Consumption of methamphetamine is on the rise and constitutes a major public health threat in the US and worldwide [13]. Methamphetamine is metabolized by cytochrome P450 (CYP) 2D6 to form amphetamine [14]. Current drug tests most commonly use urine as a matrix for assessing methamphetamine and amphetamine concentrations. Although preliminary studies have quantified the range of methamphetamine and amphetamine concentrations observed in human hair [5], no studies have assessed the rate at which amphetamine is incorporated into different hair types. However, it is not ethical to administer methamphetamine to study participants; therefore, dextroamphetamine, a common drug used for attention-deficit hyperactivity disorder (ADHD) in the US, was used as a surrogate in this study. Dextroamphetamine and methamphetamine differ only by a single methyl group. This article describes the development of a population model that

characterizes the pharmacokinetics of dextroamphetamine in the plasma and hair of healthy adults after multiple doses. The model quantifies the rate at which amphetamine is incorporated into human hair and provides a better understanding of the influence of melanin on hair pharmacokinetic parameters.

2 Methods

2.1 Subjects and Study Design

Healthy adults >18 years of age were recruited for this study, which was approved by the Institutional Review Board at the University of Utah. Demographics, including height, weight, sex, and age, were collected from each individual, and body mass index (BMI) was calculated using their height and weight measurements. Race was self-reported. As part of the inclusion criteria, subjects were given a drug test to ensure no subjects had exposure to any amphetamine. Each patient was administered 10 mg of dextroamphetamine sulfate (GlaxoSmithKline) at approximately 08:00 a.m. for 7 days. Dextroamphetamine was administered to subjects under direct supervision during week days and was self-administered over the weekend. All doses were incorporated into the model for the estimation of the pharmacokinetic parameters. Subjects were asked not to cut their hair in the vertex region of the scalp or use any form of chemical treatment on their hair during their period of participation in the study.

2.2 Sample Collection

Blood samples for analysis of plasma were collected just before the seventh dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, and 48 h after the seventh dose. Hair was collected by cutting 75–200 strands from the vertex region of the scalp at 4, 5, 6, and 7 weeks after the first dose. Hair was collected within 2 mm of the scalp and stored in aluminum foil at 20 °C, with the scalp end of the hair isolated and identified. Prior to analysis, individual strands were aligned and the 3-cm portion proximal to the scalp was isolated and used for analysis. However, due to slow hair growth, hair samples could not be collected from the same shafts of hair each week. Incorporating all hair concentrations for all 4 weeks would result in accounting for the same amphetamine concentrations in multiple samples, biasing the model. Therefore, only the week 5 hair samples were incorporated into the model to ensure that the total concentration of amphetamine in hair was flanked by blank hair on each side, resulting in all of the amphetamine deposition being accounted for in a single sample.

2.3 Plasma Analysis

Deuterated amphetamine (amphetamine-*d*₅, 2.5 ng/mL) was added to 1 mL of plasma as an internal standard. Samples were solubilized with 1 mL of 1 M NaOH overnight in a shaking water bath at 37 °C. After allowing the samples to cool to room temperature, 100 µL of NH₄OH was added to each sample. Samples were extracted with 4mL *n*-butyl chloride/ acetonitrile (4:1, v/v). Extracts were evaporated to dryness and reconstituted in 75 µL with 0.1 % aqueous formic acid/acetonitrile (95:5, v/v). Fifteen microliters were injected for analysis by liquid chromatography–electrospray ionization–tandem mass spectrometry (LC–ESI–MS/MS; SRM mode, Thermo Finnigan model TSQ® 7000) using a reverse phase high-pressure liquid chromatography column (MetaSil Basic 3 µ PNA 0516 100 × 3.00 mm;

Waters Corporation, Milford, MA, USA). The isocratic mobile phase consisted of 95 % 0.1 % aqueous formic acid and 5 % acetonitrile. The lower limit of quantitation (LLOQ) of amphetamine was 50 pg/ mL plasma. The parameters for MS/MS analysis for both amphetamine and the internal standard were as follows: collision energy of 26 %, scan width of 1.0, scan time of 0.2 s, and peak width for both Q1 and Q3 set at 0.7. The transitions for amphetamine and the internal standard were 136.2 → 91 and 141.2 → 93, respectively. Intraday and interday imprecision were <11.1 and <4.7 %, respectively, when assessed at 2.0, 6.0, 14.0, and 80.0 ng/mL of plasma. The total extraction recovery (%), assessed by fortification of drug-free hair with known concentrations of analyte at 3 and 6.0 ng/mL, was >89.5 %.

Methamphetamine, a potential contributor to biological amphetamine concentrations, was measured to ensure that plasma amphetamine concentrations were not derived from metabolism of methamphetamine. Deuterated methamphetamine (methamphetamine- d_8 , 2.5 mg) was added with amphetamine- d_5 as an internal standard. The same procedure used for the analysis of amphetamine (as described above) was also used for methamphetamine.

2.4 Hair Analysis

Deuterated amphetamine (amphetamine- d_5 , 2.5 ng/mg) was added to 10 mg of unwashed hair samples as an internal standard. Samples were solubilized with 1 mL of 1 M NaOH overnight in a shaking water bath at 37 °C. After allowing the samples to cool to room temperature, 100 µL of NH_4OH was added to each sample. Digested samples were extracted with 4 mL *n*-butyl chloride/chloroform (4:1, v/v). Extracts were evaporated to dryness and reconstituted with 0.1 % aqueous formic acid/methanol (9:1, v/v). Reconstituted samples were analyzed by LC–ESI–MS/MS using an analytical method that was the same as that used for the plasma assay except that the isocratic mobile phase consisted of 90 % 0.1 % aqueous formic acid and 10 % methanol. The LLOQ of amphetamine was 5 pg/ mg hair. Intraday and interday imprecision were < 4.3 and < 4.6 %, respectively, when assessed at 0.05, 0.50, and 5.0 ng/mg of hair. The total extraction recovery (%), assessed by fortification of drug-free hair with known concentrations of analyte at 0.05 and 5.0 ng/mg, was >90.1 %.

Deuterated methamphetamine (methamphetamine- d_8 , 2.5 mg) was added with amphetamine- d_5 as an internal standard. The same procedure was used for analysis of methamphetamine, as described above.

Hair samples were analyzed for eumelanin and pheomelanin content according to the method of Slawson et al. [2], with some minor modifications. Five milligrams of cut hair samples (1–2 mm pieces) were solubilized with 0.5 mL 57 % stabilized hydriodic acid with 20 µL of phosphoric acid and heated to 130 °C overnight. Two millilitres of 50 % ethanol was added to the cooled samples, which were then centrifuged for 15 min at 3000 rpm. Supernatants were collected and analyzed for pheomelanin content, and the remaining granules were analyzed for eumelanin content.

Pheomelanin calibrators consisted of aminohydroxyphenylalanine (AHP) in water at concentrations ranging from 25 to 600 ng/mg. After solubilization of hair samples and calibrators, the collected supernatants were evaporated to dryness in a Savant vacuum

centrifuged concentrator at 60 °C. Samples were reconstituted in mobile phase for analysis. Analysis of AHP was performed using a Waters model 600 pump controller with a Waters 717 plus autosampler and a Waters model 464 electrochemical detector (Waters Corporation). The electrochemical detector was set at +400 mV. The chromatographic column was a Luna 4.6 × 250 mm HPLC column (Phenomenex Inc., Torrance, CA, USA). The isocratic mobile phase consisted of 0.1 M sodium citrate buffer, 1 mM octanesulfonate, and 0.1 mM Na₂EDTA in water. The AHP content of the unknown samples was converted to pheomelanin content by multiplying the calculated amount of AHP by 5, as previously described [15–17].

Eumelanin granules were washed with ethanol and centrifuged at 3000 rpm for 15 min. The ethanol wash was removed and the wash repeated. Calibration curves ranging from 1 to 150 µg were prepared by suspension of sepia melanin in water to produce concentrations ranging from 0.01 to 1 mg/mL. Samples and calibrators were digested with 1 mL of 1 M NaOH with 20 µL 3% H₂O₂, heated to 100 °C for 1 h, and then centrifuged at 15,000 rpm for 3 min. Aliquots of 200 µL were measured for absorbance at 350 nm on a Cary model 2200 spectrophotometer. Quantification of unknown samples was achieved using the equation obtained by linear regression of the calibration curve plotted as absorbance at 350 nm against micrograms of sepia melanin. Sepia melanin has been determined to contain 60 % melanin [15, 18], which was factored in the final quantitation by multiplying the calculated values by 0.6.

2.5 Pharmacokinetic Analysis

Dextroamphetamine pharmacokinetic parameters were estimated using a nonlinear mixed-effects model that was implemented in NONMEM 7.2 (ICON Dev. Soln., Ellicott City, MD, USA) interfaced with PDxPOP® 5 (2010 ICON Dev. Soln.) using the first-order conditional estimation with interaction method. The dextroamphetamine plasma model was built first before incorporating the hair compartment (Fig. 1). One- and two-compartment structural models were evaluated and selected based on their goodness of fit. Model stability was assessed by altering the initial estimates for dextroamphetamine apparent clearance and apparent volume of distribution. Unstable models and those that produced erroneous results (e.g. negative parameter estimates) were disregarded. Diagnostic plots were used to assess the model's fit. Conditional weighted residuals (CWRES) were plotted versus time and population predictions using R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Models were compared by assessing the biological plausibility of the parameter estimates, the precision of the parameter estimates, and the objective function value (OFV).

Model variability and random effects were classified as one of two types of error: between-subject variability (BSV) and residual unexplained variability (RUV). BSV was assumed to be log-normally distributed according to an exponential equation:

$$P_i = \theta_{\text{pop}} \times \exp(\eta_{\text{pop}}) \quad (1)$$

where P_i is the pharmacokinetic parameter of the i th individual, θ_{pop} is the population mean for P , and η represents the normally-distributed between-subject random effect with a mean

of zero and a variance of ω^2 . Additive, proportional, combined additive and proportional, and exponential RUV error models were evaluated. The final model used a combined additive and proportional model of the form:

$$Y_{ij} = \hat{Y}_{ij}x(1 + \varepsilon_{\text{prop}}) + \varepsilon_{\text{add}} \quad (2)$$

where Y_{ij} is the observed concentration for the i th individual at time j , $\hat{Y}_{ij}$ is the individual predicted concentration, and $\varepsilon_{\text{prop}}$ and ε_{add} represent the normally-distributed proportional and additive error terms, respectively, both of which are assumed to have a mean of zero and variance of σ^2 .

2.6 Covariate Analysis

Several patient characteristics were tested for their influence on dextroamphetamine plasma and hair pharmacokinetic parameters. The covariates that were tested on the plasma compartment included current body weight, height, BMI, age, sex, and race. Covariates tested on the hair compartment included total melanin concentration (combined pheomelanin and eumelanin concentrations) and race. Total melanin concentration was included a priori in the model on the apparent volume of distribution on the basis of prior studies with basic drugs [1–3, 5–9]. Power, exponential, and linear models were evaluated for all other covariates. In addition, each continuous covariate was also evaluated after it was centered on the population mean. Forward addition was utilized to identify significant covariates. A decrease in the OFV of 3.84 was considered significant for one degree of freedom at $p = 0.05$ based on the Chi-square distribution. Backward elimination was used to remove covariates from the model, with an increase in the OFV of 6.63 corresponding to one degree of freedom at $p = 0.01$.

2.7 Model Evaluation

Base and final models were evaluated using goodness-of-fit plots. Observed drug concentrations were inspected for their correlation with predicted concentrations. The -2 and $+2$ region criterion was used to assess the CWRES plots that were constructed for the plasma and hair compartments. Uncertainty in pharmacokinetic parameter estimates was quantitatively assessed by calculating standard errors and 95 % confidence intervals for all pharmacokinetic parameter estimates. Further internal evaluations were completed using a bootstrap implemented in PDxPOP® 5. Additionally, normalized prediction distribution errors (NPDEs) were plotted against time- and population-predicted dextroamphetamine concentrations for the plasma and hair compartments individually to assess for evidence of model misspecification. Visual and numeric predictive check based on 1000 simulated datasets was performed using Perl-speaks-NONMEM (PsN, version 4.2.0; psn.sourceforge.net) interfaced with Pirana (version 2.9.0; pirana-software.com) [19]. For the visual predictive check, observation bin boundaries were set to the midpoints between target pharmacokinetic plasma sample collection times.

3 Results

A total of 40 patients with 463 plasma concentration measurements and 40 hair concentration measurements were included in this study. The demographics for the study participants at the time of the first dose are included in Table 1. The study group was predominantly male and Caucasian with varying hair colors. Plasma data were modeled first, which were well-described by a one-compartment model with first-order absorption and first-order elimination, as assessed by a significant reduction in the OFV and by the condition number (Table 2). Covariate analysis revealed that current body weight was significant on both apparent clearance and apparent volume of distribution. After inclusion of current body weight in the model, height was also found to be a statistically significant covariate on apparent volume of distribution ($p < 0.01$). However, there was no biological rationale to include height in the model, therefore it was not included in the final covariate model. Additionally, race was found to be significant on apparent volume of distribution as a categorical covariate. Unfortunately, there was not enough representation from some of the non-Caucasian races to adequately inform the model. Race was then categorized dichotomously as Caucasian or non-Caucasian, but this did not result in statistically significant changes in the model fit. Therefore, race was eliminated as a covariate. Current body weight was the only covariate that remained in the model, which was structured as follows:

$$CL/F_i = CL/F_{\text{pop}} \times \left(\frac{WT_i}{WT_{\text{pop}}} \right)^{\theta_1} \quad (3)$$

$$V_1/F_i = V_1/F_{\text{pop}} \times \left(\frac{WT_i}{WT_{\text{pop}}} \right)^{\theta_2} \quad (4)$$

where CL/F_i is the individual apparent clearance, CL/F_{pop} is the estimated population apparent clearance, WT_i is the individual current weight, WT_{pop} is the mean population current weight, and θ_1 is the estimated exponent for the effect of current weight on dextroamphetamine apparent clearance. Similarly, V_1/F_i is the individual apparent volume of distribution for the plasma compartment, V_1/F_{pop} is the population estimate, WT_i is the individual current weight, WT_{pop} is the mean population current weight, and θ_2 is the estimated exponent for the effect of current weight on dextroamphetamine apparent volume of distribution in the plasma compartment. Bootstrap results are also provided in Table 2. The bootstrap completion success rate was 99.8 %.

After plasma model development, the hair compartment was added to characterize the rate constant for dextroamphetamine incorporation from plasma into hair (K_{23}) and the apparent volume of distribution of the hair compartment (V_2/F) (Fig. 1; Table 3). However, there was only one hair concentration per patient, which made it difficult to simultaneously estimate all of the model parameters. Therefore, V_1/F was fixed to 377 L, as determined in the final plasma model. Subsequently, all the remaining parameters were successfully estimated. As

melanin concentration has been previously reported to affect the incorporation of basic drugs within hair [5], total melanin concentration was included in the model on V_2/F . After the addition of total melanin, race was also investigated as a potential covariate. Similar to the plasma model, race was significant but there were not enough representatives from each group to adequately inform the model. Creating a binary variable of Caucasian and non-Caucasian did not result in a significant change in the model. Therefore, the only covariate included in the final hair model was total melanin concentration, which was structured as follows:

$$V_2/F_i = V_2/F_{\text{pop}} + \theta_3 \times \text{total melanin} \quad (5)$$

where V_2/F_i is the individual apparent volume of distribution for the plasma compartment, V_2/F_{pop} is the population estimate, and θ_3 is the estimated slope for the effect of total melanin on dextroamphetamine volume of distribution in the hair compartment. A bootstrap was conducted for internal evaluation, with a completion success rate of 95.2 % (Table 3).

Diagnostic plots for the final linked model were visually inspected to confirm the final model suitability (Fig. 2), and CWRES and NPDE plots were used to further evaluate the model (Figs. 3 and 4, electronic supplementary Fig. 1). Additionally, data were simulated to produce a visual predictive check comparing the 5th, 50th, and 95th percentiles for the plasma compartment (Fig. 5). A numeric predictive check indicated that 92.6 % of the plasma observations fell within the 90 % prediction interval based on the simulations, demonstrating acceptable agreement between observed and predicted concentrations of dextroamphetamine.

4 Discussion

This is the first population model to describe dextroamphetamine pharmacokinetics in a plasma model linked to hair. Additionally, this is the first model to report the rate constant for dextroamphetamine incorporation within human hair. This study demonstrated that the pharmacokinetics of dextroamphetamine were well-described by a single plasma compartment linked to a single hair compartment, with first-order absorption and elimination. The population means were estimated as follows (Table 3): $K_{12} = 0.527 \text{ h}^{-1}$; $\text{CL}/F = 28.7 \text{ L/h}$; $V_1/F = 377 \text{ L}$; $K_{23} = 1.60\text{e-}6 \text{ h}^{-1}$; and $V_2/F = 17.7 \text{ mg}$. Covariate analysis indicated that current body weight was a significant covariate on CL/F and V_1/F (Eqs. 3 and 4). In addition to current body weight, height was also found to be a statistically significant covariate on V_1/F ; however, there was no biological evidence to suggest that height should influence V_1/F . Originally, it was believed that height might be serving as a proxy for another covariate, such as sex or BMI; however, neither of these covariates significantly affected the model. It is possible an additional unmeasured characteristic could explain this observation. Nevertheless, without sufficient physiological rationale to support height as a covariate, it was not included in the final model.

Further covariate analysis also indicated that race was a significant covariate on V_1/F and V_2/F . Amphetamine is metabolized by CYP2D6 [20], which is a highly polymorphic CYP

[21]. Additionally, race has been shown to influence the minor allele frequency of CYP2D6 polymorphisms [22]. Therefore, it stands to reason that race could play a significant role in the pharmacokinetics of dextroamphetamine. Statistical analysis of race as a covariate indicated it was significant; however, this study was not powered with enough participants from each race to truly inform the model. Of the 40 participants, only 15 were not Caucasian; therefore, this covariate was not included in the final model. However, further study is warranted to determine the influence of race on the pharmacokinetics of dextroamphetamine or other amphetamine derivatives in plasma and hair.

Total melanin concentration was found to be a significant covariate on V_2/F (Eq. 5). In fact, without the addition of this covariate, the model would not populate, suggesting a high correlation between total melanin concentration and V_2/F . Higher melanin concentrations correlated with lower V_2/F predictions. This supports the notion that differences in hair color should be taken into account when determining permissible amphetamine or amphetamine derivative concentrations for illicit drug testing in hair. Additionally, this study demonstrates a very slow incorporation rate from plasma into hair (Table 3) that is most likely attributable to hair growth, which supports the widely accepted notion that hair should only be considered in testing for evidence of sustained or chronic amphetamine use.

There are some limitations to the modeling approach employed in this study that should be noted. Washed and unwashed hair samples were available for analysis; however, after investigation into these samples, it was noted that the unwashed samples followed an expected concentration–time curve, in which concentrations peaked at week 5 and slowly decreased in weeks 6 and 7. In contrast, concentrations from the washed samples were random and did not follow any trend. Therefore, there was a concern that the washing method may have been too stringent and removed amphetamine from the hair shaft. As a result, washed samples were excluded from the analysis and only unwashed samples were incorporated into the model. However, a limitation of this approach is that the concentrations measured in these unwashed samples could also reflect some contribution from sweat and/or sebum that were not actually incorporated into the shaft. Additionally, the concentration of amphetamine reported in the 3-cm sample of hair was normalized to the entire weight of the 3-cm sample. There was hair in this sample that did not have any amphetamine incorporation; therefore, the concentrations of amphetamine in hair actually harboring the drug were likely higher than those used in the model. However, because it was not possible to know which parts of each strand of hair actually contained the amphetamine, concentrations had to be normalized to the entire sample of hair. Finally, the rate at which amphetamine was incorporated into hair reported in this study applies to an administration of amphetamine once daily for 7 days. However, now that this has been quantified for this particular situation, simulations of other administration schedules could now be performed to predict what the rate of amphetamine deposition into hair would be in other scenarios.

5 Conclusions

This is the first study to describe the pharmacokinetics of dextroamphetamine in a population model with a hair compartment. Furthermore, this is the first study to describe the rate at which amphetamines are deposited into hair after multiple doses. The findings

reported herein lay the groundwork to potentially inform pharmacokinetic analyses for other amphetamine derivatives that are of common interest in illicit drug testing, particularly when hair is used as a matrix.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

This is the first linked population study that simultaneously describes the pharmacokinetics of dextroamphetamine in plasma and hair.

Dextroamphetamine in plasma was modeled with a one-compartment model. Weight centered on the mean was significantly associated with the apparent clearance and volume of distribution.

High melanin concentrations were associated with a smaller dextroamphetamine volume of distribution in the hair.

Fig. 1.

Final linked dextroamphetamine model schematic. K_{12} rate constant from the gut compartment to the plasma compartment, V_1/F apparent volume of distribution of the plasma compartment, CL/F apparent clearance from the plasma compartment, K_{23} incorporation rate constant from plasma to hair, V_2/F apparent volume of distribution of the hair compartment

Fig. 2.

Diagnostic plots for the final linked dextroamphetamine covariate model. Observed versus **a** population-predicted and **b** individual-predicted dextroamphetamine plasma concentrations, and observed versus **c** population-predicted and **d** individual-predicted dextroamphetamine hair concentrations. The *solid black lines* depict the lines of identity ($y = x$), and the *dashed black lines* depict the LOESS fits of the data

Fig. 3.

Diagnostic plots for the final linked dextroamphetamine covariate model. Conditional weighted residuals of dextroamphetamine plasma concentrations versus **a** time since previous dose and **b** population-predicted concentrations. Conditional weighted residuals of dextroamphetamine hair concentrations versus **c** time since previous dose and **d** population-predicted concentrations. The *solid black lines* depict $y = 0$

Fig. 4.

Diagnostic plots for the final linked dextroamphetamine covariate model. Normalized prediction distribution errors of dextroamphetamine plasma concentrations versus **a** time since previous dose and **b** population-predicted concentrations. Normalized prediction distribution errors of dextroamphetamine hair concentrations versus **c** time since previous dose and **d** population-predicted concentrations. The *solid black lines* depict $y = 0$

Fig. 5.

Visual predictive check for the final linked dextroamphetamine covariate model.

Observations are depicted as *gray dots*. The *solid black line* depicts the observed 50th percentile, and the *dashed black lines* depict the observed 5th and 95th percentiles. The *shaded regions* depict the 95 % confidence intervals surrounding the predicted 5th, 50th, and 95th percentiles

Table 1

Demographics of the 40 study participants who received dextroamphetamine 10 mg daily for 7 days

Characteristics	<i>n</i> (%) or mean $\pm$ SD (range)
Male	29 (73)
Female	11 (27)
Current weight, kg	78.8 $\pm$ 12.1 (56.6–113)
Height, cm	176.9 $\pm$ 10.3 (154.9–195.6)
Age, years	26.6 $\pm$ 4.9 (21–40)
Body mass index, kg/m ²	25.3 $\pm$ 3.8 (19.3–34.7)
Race	
Caucasian	25 (63)
Asian	9 (22)
Hispanic/Latino	4(10)
African American	2(5)
Hair color	
Black	17 (43)
Brown	11 (28)
Red	7 (17)
Blond	5 (12)

SD standard deviation

Table 2

Plasma dextroamphetamine model parameter estimates

Parameters	Final plasma model				Bootstrap ($n = 1000$)			
	Mean parameter estimate	SE	Lower CI	Upper CI	Mean parameter estimate	SE	Lower CI	Upper CI
K_{12} (h^{-1})	0.533	0.0338	0.467	0.599	0.534	0.0352	0.470	0.608
V_1/F (L)	377	26.0	326	428	374	30.8	304	430
θ_1	0.800	0.205	0.398	1.20	0.81	0.233	0.322	1.28
CL/F (L/h)	28.3	1.15	26.0	30.6	28.3	1.16	26.3	30.9
θ_2	0.512	0.189	0.142	0.882	0.54	0.217	0.137	1.00
ω^2 -BSV								
K_{12}	0.0394	0.0252	-0.00999	0.0888	0.021	0.0202	2.00E-06	0.0702
V_1/F	0.0407	0.0216	-0.00164	0.0830	0.0356	0.0199	0.00443	0.080
CL/F	0.0394	0.0252	-0.00999	0.0888	0.0392	0.0251	0.00862	0.100
σ^2 -RUV								
Additive (ng/mL)	0.326	0.265	-0.193	0.845	0.683	1.30	0.0195	5.91
Proportional	0.0601	0.0107	0.0391	0.0810	0.0570	0.0148	0.0116	0.0802

SE standard error, CI 95 % confidence interval, K_{12} absorption rate constant, V_1/F apparent volume of distribution of the plasma, θ_1 estimated exponent on current weight (kg) centered on the mean for V_1/F , CL/F apparent clearance of the central compartment, θ_2 estimated exponent on current weight centered on the mean for CL/F , ω^2 -BSV between-subject variability, σ^2 -RUV residual unexplained variability

Table 3

Final linked plasma and hair dextroamphetamine model parameter estimates

Parameters	Final linked model				Bootstrap ($n = 500$)			
	Mean parameter estimate	SE	Lower CI	Upper CI	Mean parameter estimate	SE	Lower CI	Upper CI
K_{12} (h ⁻¹)	0.527	0.0303	0.467	0.586	0.541	0.0891	0.466	0.991
V_1/F (L)	377 (fixed)	NA	NA	NA	NA	NA	NA	NA
θ_1	0.618	0.166	0.293	0.943	0.562	0.261	0.00600	0.953
CL/F (L/h)	28.7	0.840	27.1	30.3	28.6	0.874	27.0	30.4
θ_2	0.422	0.197	0.0359	0.808	0.419	0.260	0.00400	0.930
K_{23} (h ⁻¹)	1.60E-06	2.76E-07	1.06E-06	2.14E-06	15.6	2.70E-07	1.02E-06	2.07E-06
V_2/F (mg)	17.7	2.62	12.6	22.8	17.3	2.23	11.6	19.8
θ_3	-1.05E-03	1.52E-04	-1.35E-03	-7.52E-04	-1.02E-03	1.34E-04	-1.20E-03	-7.00E-04
ω^2 -BSV								
K_{12}	0.0106	0.0316	-0.0513	0.0725	0.0304	0.0766	1.00E-06	0.368
CL/F	0.0212	0.00833	0.00487	0.0375	0.0209	0.00863	0.00688	0.0410
σ^2 -RUV								
Additive (ng/mL)	0.404	0.190	0.0316	0.776	0.381	0.173	0.0502	0.754
Proportional	0.104	0.00986	0.0847	0.123	0.1030	0.00947	0.0821	0.120

SE standard error, *CI* confidence interval, *NA* not applicable, K_{12} absorption rate constant, V_1/F apparent volume of distribution of the plasma, θ_1 estimated exponent on current weight (kg) centered on the mean for V_1/F , CL/F apparent clearance of the plasma compartment, θ_2 estimated exponent on current weight centered on the mean for CL/F , K_{23} rate constant from plasma to hair compartment, V_2/F apparent volume of distribution of the hair, θ_3 estimated slope on total melanin concentration for V_2/F , ω^2 -BSV between-subject variability, σ^2 -RUV residual unexplained variability