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Population pharmacokinetics modeling of two methylphenidate formulations in plasma and saliva of healthy subjects

Submitted

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ABSTRACT

Monitoring methylphenidate (MPH) concentrations can help determine whether a lack of observed efficacy and/or the presence of unexpected adverse effects are related to pharmacokinetic (PK) or pharmacodynamic (PD) factors. Saliva sampling is a promising non-invasive alternative to blood sampling, particularly in children. However, the challenges associated with reliably predicting MPH plasma concentration from a saliva sample has limited the feasibility of using saliva sampling to monitor MPH plasma concentration. Here, we investigate and quantify putative sources of variability in MPH plasma and saliva concentrations and describe the saliva-to-plasma relationship using nonlinear mixed-effect population PK modeling. In this randomized, open-label study, immediate-release MPH (MPH-IR) and osmotic release oral system MPH (MPH-OROS) were administered in a crossover design to 12 healthy adult subjects (six men and six women). Paired blood and saliva samples were collected pre-dose and at regular intervals for 6 (MPH-IR) or 11 (MPH-OROS) hours following drug administration. Population PK analysis was performed using nonlinear mixed-effect modeling. A one-compartmental structure model with first-order absorption (with separate compartments for MPH-IR and MPH-OROS) and first-order elimination provided the best description of estimated MPH plasma PK. The estimated clearance was 6.0 liters/hour and the volume of distribution was 7.5 liters. The derived terminal half-life was 0.9 hours. Inter-individual variability was identified on clearance, the volume of distribution, and the absorption rate constant for MPH-OROS. The saliva-to-plasma MPH (S/P) ratio was 2.44 from 2.5 hours onward. Inter-individual variability was identified in the S/P ratio. With proper allometric scaling techniques, we expect that this PK model can used in children to predict the concentration-time profile in the plasma using MPH concentrations measured in saliva samples.
Introduction

Methylphenidate (MPH) is currently the medication of choice for treating patients with attention-deficit/hyperactivity disorder (ADHD), a highly prevalent neurodevelopmental disorder that places significant burdens on social development and can impede academic performance. Although controlled trials have found that 60-70% of children respond to MPH, actual clinical experience has revealed a much lower and less predictable response rate of approximately 50%. The clinical use of MPH is usually based on a trial-and-error approach before optimal therapy is achieved, as MPH has wide inter-individual variability in terms of both plasma concentrations and clinical response. Approximately 20-30% of patients do not respond favorably to MPH at any dose, and these so-called ‘non-responders’ must switch to an alternative medication after this initial attempt at treatment. Therefore, a significant subset of children with ADHD experience a delay in receiving adequate treatment, and patients may stop taking medication altogether. A clear view of MPH concentration-time profiles is needed in order to understand whether a lack of observed efficacy and/or the presence of unexpected adverse effects is related to pharmacokinetic (PK) or pharmacodynamic (PD) factors. However, measuring circulating MPH concentration in children is extremely challenging due to the need for repeated intravenous blood sampling.

Collecting samples for measuring drug concentrations should be performed with minimal discomfort to the patient, particularly in pediatric patients. Because MPH is a weak base (with a pKₐ of 8.9) and has a relatively low molecular weight (233 Da), it diffuses readily across cell membranes and other lipid layers, quickly entering tissues and biological substrates that are more acidic than blood, thus enabling its detection in other matrices at relatively higher concentrations. Moreover, because of its low protein binding saturation (10-33%), nearly all of the total MPH available in the plasma can diffuse to extravascular compartments. Several non-invasive biological matrices for measuring MPH have been proposed, including urine, breath, sweat, hair, and saliva. Saliva sampling is currently the most promising non-invasive alternative to blood sampling, as it allows for the determination of concentration-time profiles of both MPH and the ritalinic acid metabolite. However, several potential complicating factors have been encountered in previous studies, including indications of oral contamination in the first few saliva samples after taking MPH tablets and considerable variation in the saliva-to-plasma (s/p) ratio throughout the time course of both tablet and capsule formulations. Nevertheless, if the sources of variability in the s/p ratio could be minimized or quantified, saliva drug sampling has the potential to become a reliable alternative to plasma drug sampling.

Here, our primary objective was to use population-approach modeling techniques to describe the concentration-time profile of MPH in plasma and saliva after oral administration of MPH-IR and MPH-OROS in healthy adult subjects. Our secondary objective was to quantify the degree of contamination in the early saliva samples and to determine the effect of saliva pH on MPH saliva measurements, as MPH’s ionized free fraction may be incorporated into saliva as has been described for other weak bases, including amphetamine-type substances.

Methods

Clinical trial

This trial was a randomized, open label, two-way crossover study performed in 12 healthy adult subjects (6 men and 6 women). Based on our previous experience, we expected that a sample size of 12 subjects would be sufficient for determining the PK parameters and s/p ratio. The study was conducted in accordance with the International Conference on Harmonisation’s Guidelines for Good Clinical Practice and in accordance with the tenets of the Declaration of Helsinki. The study was performed at the Centre for Human Drug Research in Leiden, the Netherlands, and approved by the local ethics committee of Leiden University Medical Center (Leiden, the Netherlands). The subjects...
provided written informed consent after receiving a full explanation of the study. Subjects had to be healthy, 18-35 years of age, with a body mass index of 18-30 kg/m² and body weight of 50-90 kg. Subjects had to use a medically approved method of contraception throughout the entire study period and for three months after the study was completed.

We excluded subjects with a clinically relevant abnormal history of physical or mental health determined from the subject’s medical history and physical examinations (obtained during the screening visit and/or prior to receiving the first dose of the study drug); clinically relevant abnormal laboratory results, ECG, vital signs, or physical findings; current breast-feeding; and/or a history of alcohol and/or substance abuse within three years of screening. Subjects who habitually consumed more than 21 or 14 units of alcohol per week, respectively, and subjects who smoked >5 cigarettes/day or used nicotine or nicotine-containing products within three months of screening were excluded. We also excluded subjects who tested positive for hepatitis B, hepatitis C, or HIV, female subjects with a positive urine-based pregnancy test, and subjects who tested positive for drug and/or alcohol at screening. Subjects with previous exposure to pharmaceutical stimulants (including— but not limited to MPH, MDMA, methamphetamine, amphetamine, ephedrine, and cocaine) in the past six months were excluded, as were subjects who took any medication other than ibuprofen, paracetamol, oral contraceptives, or topical medication within one month of their first dose of the study drug; clinically relevant abnormal laboratory results, ECG, vital signs, or physical findings; current breast-feeding; and/or a history of alcohol and/or substance abuse within three years of screening. Subjects who began their treatment by taking Ritalin (immediate release MPH) and Concerta (osmotic controlled-release oral delivery system MPH) formulations were chosen as interventions, as most Dutch children with ADHD begin their treatment by taking Ritalin (MPH-IR, Novartis Pharmaceuticals UK Ltd.), and Concerta (MPH-OROS, Janssen-Cilag Ltd.) was the most commonly used extended-release formulation at the time of the study (CSP database 2011, Genees- en hulpmiddelen Informatie). Each subject randomly received either 10 mg of MPH-IR (Ritalin) or 18 mg MPH-OROS (Concerta) on different study days separated by a minimum of five days. The potential effects of the estrous cycle on MPH pharmacokinetics has not been evaluated in humans. Therefore, female subjects who took oral contraceptives were studied while taking their contraceptive but not in the stop week. Subjects were required to refrain from consuming xanthine- and/or alcohol-containing products and from smoking within 12 hours of MPH administration until the end of each study day. On study days, the subject was questioned regarding his/her intake of medication, alcohol, and/or illegal drugs, and a urine drug screen, a urine-based pregnancy test, and an alcohol breath test were performed before any study-related procedures began. The MPH dose was taken with 240 ml water after an overnight fast of ≥10 hours.

Subjects were instructed not to chew the medication and to swallow the tablet or capsule whole. Subjects were confined to the clinical research unit for approximately six (MPH-IR) or 12 (MPH-OROS) hours after drug administration. Water (250 ml) was provided every two hours after the MPH dose to maintain all subjects on a consistent hydration schedule. A standardized lunch (MPH-IR) or lunch and dinner (MPH-OROS) was provided 4 and 10 hours, respectively, after the MPH dose.

To measure the PK of MPH-IR, saliva and blood samples were collected pre-dose and at t=20, 40, 60, 80, 100, 120, 150, 180, 210, 240, 300, and 360 minutes after the dose. To measure the PK of MPH-OROS, saliva and blood samples were collected at the same time points as well as at the following additional time points: t=270, 330, 360, 420, 450, 480, 600, and 720 minutes. Saliva samples were obtained actively using the Polyester Salivette swab system (Sarstedt AG, Nümbrecht, Germany), a commercially available product designed specifically for collecting saliva specimens. The system contains a roll of polyester that is held in the oral cavity for several minutes. Three swabs were collected per time point. Saliva was collected actively in order to minimize variability in saliva pH. After collection and weighing the saliva (to assess salivary flow), the swabs were immediately centrifuged at 2000×g for 10 minutes at 4 °C. Subsequently, the saliva collected from the three swabs was pooled, and pH was measured.
using a Symphony pH meter (model SP70P, VWR Scientific) fitted with a pH/Redox electrode (pH range: -2.000 to 19.999; relative accuracy: ± 0.002). Finally, the sample was divided in two, transferred to 2-ml tubes (Sarstedt), and immediately stored at -80°C. One stored sample was used for analysis, and the other sample was stored as a back-up. Blood samples were collected in 6-ml EDTA tubes to inhibit plasma esterases, which metabolize MPH to ritalinic acid. The blood samples were cooled in an ice bath and centrifuged at 2000×g for 10 minutes at 4°C within 30 minutes of collection. The plasma fractions were collected, aliquoted into two transport tubes (containing approximately 1 ml of plasma per tube) and stored at -80°C.

Quantification of saliva and plasma MPH concentration

MPH (and the internal standard d9-MPH) was analyzed in plasma and saliva samples by liquid chromatography–tandem mass spectrometry (LC–MS/MS) using the positive ionization mode of a Thermo Scientific (Waltham, MA, USA) Surveyor LC coupled to a Thermo Scientific Quantum Access MS. The development and validation of this LC–MS/MS method using hydrophilic interaction liquid chromatography for MPH analysis and for assessing MPH stability in plasma and saliva at various temperatures have been described previously15. The assay’s lower limit of quantification (LLOQ) was 0.5 µg/l in both plasma and saliva.

Population model development

DATA

Exploratory individual and summary concentration-time profiles were generated in order to identify potential outliers, to understand the possible effect of censoring concentrations below the LLOQ, and to provide indications regarding the base structural model. All concentrations below the LLOQ after Tmax were excluded from the analysis. All concentrations below the LLOQ prior to Tmax were set to zero.

MODELING STRATEGY

Population PK analysis was performed by nonlinear mixed-effect modeling using NONMEM version 7.2.0 (Icon Development Solutions, Ellicott City, MD, USA). The model was developed using ADVAN with First-Order Conditional Estimation with Interaction (FOCEI). Different models were compared with increasing complexity in the structural model and by increasing the number of random effects. The objective was to obtain the simplest model that described the data adequately. NONMEM reports an objective function value (OFV), which is the -2 times log likelihood (-2LL). Models were compared using the likelihood ratio test, with the assumption that the difference in -2LL is Chi-square distributed, with degrees of freedom determined by the number of additional parameters in the more complex model. Hence, with a decrease in OFV of at least -6.63 points (p<0.01), the model with one additional parameter was preferred over its parent model. We also used graphical analyses to help assess the differences between models. These analyses included: (1) predicted concentration versus observed concentration; (2) Conditional Weighted Residuals with interaction (cwresi) versus predicted concentration, as well as cwresi versus time; (3) frequency distribution of the post hoc individual estimates of ETAs; and (5) correlation plots of post hoc individual estimates of ETAs of all parameters with a random effect. The statistics software package R was used for graphical representations to evaluate of the goodness of fits, to select covariates, and to evaluate the models.

Population PK MODEL DEVELOPMENT

The population PK analysis focused on identifying structural (e.g., 2 and 3 compartmental) models with appropriate absorption and elimination processes (e.g., linear or nonlinear) to best describe and explain all of the collected data. The population parameter estimates were incorporated using In-normal distributions. Additional, proportional or combined additive and proportional residual error distributions were drawn using parameters from a normal distribution to describe the residual variability. The random effects structure was incorporated using In-normal distributions for the inter-individual variability.
(iiv) of the PK parameters. The iiv of the PK parameters were established by applying an exponential transformation of a normal random effects distribution. Various types of variance-covariance matrices were tested for iiv. The estimated population values (both fixed and random effects) were used to determine individual empirical Bayes’ estimates (post hoc estimates) of the PK parameters. The best structural PK model was determined before any covariate (e.g., sex, weight, or height) was evaluated for incorporation into the model. To visualize potential correlations, scatter plots were created for each pair of covariates with a variance-covariance ellipse, the Pearson correlation coefficient, and its significance. This approach was performed to assess correlations between covariates, correlations between post hoc individual estimates of ETA for each parameter and the covariate, and between estimated PK parameters and covariates. Confounding covariates were grouped following an evaluation of their correlation structure. The covariate in each variable cluster that had the highest correlation with the empirical Bayes’ estimates of the parameters—and which was also clinically relevant—was implemented in the model. Continuous covariates were included by centering on a reference value; the median of the observed covariate values was selected as the most informative reference value.

The model was developed using a sequential approach in which plasma MPH PK was modeled first. Subsequently, a saliva MPH PK model was developed in which all plasma PK parameters were fixed to the individual estimates derived from the plasma PK model.

Results

Subjects

Twelve healthy adult subjects (6 men and 6 women) met the selection criterion and were enrolled in the study. The mean age of the subject was 23 years (range: 19–31 years), and the subjects had a mean body mass index of 22.1 kg/m² (range: 19.7–26.6 kg/m²). All subjects tested negative for pre-dose drugs of abuse in the urine. Concomitant medication used during the study period included ibuprofen (400 mg orally four days prior to the study day) and paracetamol (500 mg orally eight days after the last dose). All 12 subjects completed the study.

Pharmacometrics analysis

POPULATION PK PLASMA MODEL DEVELOPMENT

A total of 764 plasma samples were obtained from the 12 subjects. Fewer than 20% of the samples had PK data below LOQ. Based on the exploratory plots, one outlier (a plasma sample taken five hours after the administration of an MPH–IR dose) was excluded from the analysis. After the administration of MPH–IR and MPH–OROS, the concentration-time profiles of subject 8 and subject 9 deviated from the profiles of the other subjects; however these data remained in the dataset.

DEVELOPMENT OF THE POPULATION PK PLASMA MODEL

The plasma PK data were described best by a one-compartment PK model with separate absorption compartments for the two drug formulations. The best model is depicted schematically in Figure 1. We estimated the lag time between administration of the drug and the onset of absorption (ΔlAC). For the MPH–OROS formulation, absorption was divided into two first-order absorption processes; one standard oral absorption process reflecting the capsule’s immediate-release component, with its own lag time and the same $ka_1$ as the IR formulation ($oros_{ir}$), and an additional absorption process reflecting the capsule’s slow-release component ($oros_{sr}$), which was defined as a continuous infusion with a distinct lag time and $ka_2$. This approach required the estimation of an infusion rate ($r_3$). To parse the MPH–OKOS dose into the $oros_{ir}$ and $oros_{sr}$ components, the fraction of the dose corresponding to $oros_{ir}$ was modeled in terms of bioavailability ($F$), and the remaining fraction of the dose (corresponding to $oros_{sr}$) was defined as $(1-F)$. The central compartment was
defined in terms of distribution volume ($V$) and clearance ($CL$). Ultimately, we abandoned our attempts to model IR and oros $ir$ as one compartment, as this resulted in worse fit and a non-normal distribution of the individual $CL$ parameters (in which $CL$ was formulation-dependent) and conditional weighted residuals. IIV was identified for $CL$, $V$, and $ka_2$. Based on the correlation scatter plots, age and sex were considered as covariates for $CL$, $V$, and $ka_2$: these were not incorporated in the model as they did not result in an improvement in OFV. Covariance between $V$ and $ka_2$ improved the model’s performance and was therefore kept in the model. The estimated $PK$ parameters of the best $PK$ plasma model are summarized in Table 1. Parameter estimations are accurate given the relatively low standard deviations, except for the absorption rate constants that show higher, but acceptable standard deviations. With regard to the goodness-of-fit plots (Figure 2), the observations versus population predictions indicate that the structural model is appropriate, as inclusion of the IIV (individual predictions) improves the goodness-of-fit, e.g. the observations are closer to the line of unity. In general, the conditional weighted residuals versus the population prediction and versus time are symmetrically distributed around zero indicating good model performance. However, there is a small – albeit acceptable – bias in the low concentration range near time=0. Overall, the conditional weighted residuals are normally distributed (Figure 2). The individual plasma MPH concentration versus time after administration of MPH-IR and MPH-oros are well described by the model, with exception for subjects 8 and 9 (Figure 3).

**Development of the Population PK Saliva Model**

A total of 612 saliva samples were obtained from the 12 subjects. Fewer than 20% of the samples had $PK$ data that was below LOQ. The saliva samples collected after administration of MPH-IR (tablet formulation) had clear indications of contamination, and efforts to correct for this contamination resulted in major bias in the description of the terminal $PK$ phase. Based on previous experience in similar studies (our unpublished data), we excluded all post-dose MPH-IR data collected prior to the 2.5-hour post-dose time point.

The saliva $PK$ data were described best as a linear relationship between MPH concentration in the plasma and MPH concentration in the saliva. The individual plasma MPH drug concentrations at each time point were used to drive the saliva model, with the following equation:

$$Y = \alpha \times C_P$$

where $Y$ is the saliva MPH concentration, $C_P$ is the plasma MPH concentration, and $\alpha$ is the estimated parameter ($s/p$ ratio).

The estimated $s/p$ ratio ($\alpha$) was 2.44 (± standard error 26.9%). The residual error was described best by a proportional error structure (0.171 ± standard error 13%). IIV could be identified for $\alpha$ (0.14 ± standard error: 2.9%). No covariate relationships could be identified (for example, saliva pH or flow were not identified as covariates).

As with the best $PK$ plasma model, the predicted concentrations in the best $PK$ saliva model were accurate with a small – albeit acceptable – bias in the low concentration range (Figure 4). The first samples also had a time-dependent bias (Figure 4). CWRESi was distributed normally, with 0 lying within the 1.5 interquartile range, despite the presence of some outliers at the extremes of the distribution (Figure 5); these outliers remained when the data were separated by formulation (data not shown). The outliers at the extremes were more evident for MPH-oros than for MPH-IR. With the exception of the data collected from subjects 8 and 9 following MPH-IR administration, the model describes the data adequately (Figure 6).

**Discussion**

Reliable prediction of plasma MPH concentrations based on saliva sampling is challenging. As a result, the feasibility of this method has been questioned. Minimizing and quantifying sources of variability in the saliva/plasma ($s/p$) ratio could improve the acceptance of serial saliva sampling as an alternative to therapeutic drug monitoring using (invasive) serial plasma sampling, which
is of particular interest in pediatric populations. Here, a first attempt was made to quantify sources of variability in MPH plasma and saliva concentrations, and to describe the relationship between MPH concentration in saliva and MPH concentration in plasma using a population PK modeling approach. The data were comprised of paired plasma and saliva MPH concentrations from healthy adults, following a single dose of MPH–IR (through 6 hours post-dose) or MPH–OROS (through 24 hours post-dose).

A one-compartment model with first-order absorption (separate absorption compartments for MPH–IR and MPH–OROS) and first-order elimination best described the plasma PK for MPH. The population parameter estimates for clearance was 403 liters/hour with a distribution volume of 1808 liters and a derived terminal half-life (ln2/ke) of 3.15 hours, which is consistent with previously published estimates. The population parameter estimates for clearance, distribution volume, and lag time (for the IR formulation) had low uncertainty; however, the standard errors of the population values for the absorption rate constants of both MPH–IR and MPH–OROS, as well as the standard error for the lag time of the sustained release phase of MPH–OROS, were relatively high, albeit still within an acceptable range. Absolute bioavailability after oral dosing has been reported to be both low and variable. The level of uncertainty for ka’s and lag time may be explained—at least in part—by the relatively low number of subjects, lack of data points in the upward part of the concentration time profile and the seemingly aberrant PK profiles of two subjects, particularly after receiving the MPH–IR formulation. For example, the post-MPH–IR dose plasma concentrations in subject 9 had an extremely long absorption phase, which may be attributed to extended gastric emptying time, which is the primary factor controlling MPH absorption for IR formulations. Because gastric emptying time can be prolonged in both clinical and research settings, we did not exclude these data from our analysis. In addition, large differences between subjects have been reported with respect to the release profile of MPH–OROS. Finally, our model described absorption during the osmotic release phase of MPH–OROS capsules as a continuous, stable infusion. In contrast, the rate of release from OROS capsules has been reported to increase over time due to the drug’s concentration gradient that is incorporated into the two layers. Therefore, the model’s descriptive properties might be improved further by incorporating previously published data—for example, the average release profile of MPH–OROS capsules—into the model.

Given MPH’s physicochemical characteristics, it is likely that MPH is incorporated into the saliva by passive diffusion of the free ionized drug fraction, which will become ionized in saliva and therefore cannot diffuse back into the plasma. A small—but acceptable—bias in the low concentration range was observed in saliva, which was likely due to the similar bias in the plasma PK model and oral contamination in the saliva samples collected early after MPH–IR administration. Our data set included some subjects who had contamination in their early samples (i.e., some or all of the subjects after taking MPH–IR) and subjects who had no contamination (i.e., all of the subjects after taking MPH–OROS); by inference information collected after taking MPH–OROS could theoretically provide information regarding possible contamination after taking MPH–IR. Such contamination would be the strongest—and therefore would have the highest impact on PK parameters—at earlier time points. Our efforts to correct for oral contamination resulted in a large bias in the description of the terminal phase. Therefore, a pragmatic approach was chosen: all saliva data collected in the first 2.5 hours after administration were excluded from analysis.

Obtaining an accurate s/p ratio is essential for realizing the full potential of using saliva sampling to monitor plasma MPH concentrations. The theoretical s/p ratio based on the modified Henderson–Hasselbalch equation has previously been calculated as 3.1. In our study, the model–based s/p ratio for MPH at time points beyond 2.5 hours after administration averaged 2.44. This value is lower than the average s/p ratios reported in previous studies, which may be explained by study-related differences in saliva stimulation. Because stimulating saliva secretion increases the saliva’s pH to values that approach plasma pH, the apparent drug concentration of basic drugs can be reduced, and resulting s/p ratios will have less variability, for example as described previously for MDMA and cocaine. Therefore, we obtained the saliva samples
actively using a mechanical stimulus (which can stimulate saliva flow of 1–3 ml/min\textsuperscript{28}). In contrast, in a previous study\textsuperscript{12} samples were collected by having the subject spit, which usually produces little stimulation, thus leading to higher apparent drug concentrations and higher $s/p$ ratio variability. As basal (i.e., unstimulated) salivary flow is generally lower in children with ADHD than in children without ADHD\textsuperscript{29}, stimulating salivary flow with active sampling may be even more important in this patient population in order to ensure adequate sample volume for analysis. The $s/p$ ratios in our study had inter-individual variability. For strong basic drugs such as methamphetamine, the $s/p$ ratio can be highly sensitive to small changes in saliva pH, and inter-individual variability in saliva pH is the likely explanation for inconsistent $s/p$ ratios with these drugs types\textsuperscript{30}. However, both saliva pH and saliva flow could not be identified as covariates in the current dataset.

Our results serve as the impetus for exploring further the feasibility using saliva as a non-invasive method for monitoring MPH concentrations in patients, particularly children. Because this method has the added benefit of allowing on-site testing without the need for medical personnel or complicated sample processing, the burden of collecting samples from children is decreased even further. Using saliva sampling to measure MPH concentration is currently limited to confirming treatment compliance or testing for treatment misuse. However, monitoring MPH saliva concentrations in children with ADHD could have several important clinical and research applications. For example, the time course of clinical efficacy parameters in children can be simulated based on the time course of MPH concentration in adults\textsuperscript{32}. If our model is validated for children using pediatric PK data, the true parameters of the pediatric PK-PD relationship could be estimated, and the model could be used to estimate target MPH concentrations > 2.5 hours after administration in the pediatric population. Such a result would represent an important step towards using non-invasive therapeutic drug monitoring to provide customized treatment to children with ADHD. Ultimately, the ability to differentiate between responders and non-responders—ideally at the onset of MPH treatment—would help clinicians determine which medication, dose, and formulation will likely work best in each child with ADHD. In addition, our PK model could be used to simulate a clinical trial in order to determine the optimum sampling schedule for future studies.

Despite its advantages, several issues may limit the potential applicability of our method. In our study, concomitant medication shortly before and/or during study days was limited to the use of only a few medications, including ibuprofen and paracetamol. Children with ADHD often use medications that are related—either directly or indirectly—to ADHD treatment or the treatment of psychiatric comorbidities; such medication include tricyclic antidepressants and other antidepressants, clonidine, antipsychotics, antiepileptic agents, anxiolytics, melatonin, and other hypnotics\textsuperscript{32}. Thus, validation studies are needed to in order to determine the predictive performance of our model in patients who use these medication types.

In conclusion, we report that the relationship between plasma and saliva MPH concentrations in healthy adult subjects can be described as a constant $s/p$ ratio, but only 2.5 hours after administration of two distinct oral formulations of MPH. With proper allometric scaling (using body size to account for developmental changes in MPH clearance and distribution volume), this PK model may also be suitable for predicting the concentration-time plasma MPH profile in children using non-invasive saliva sampling. Further studies are needed to determine the predictive performance of the model in children with ADHD.
REFERENCES
TABLE 1  Parameter estimates of the best plasma MPH PK model.

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<th>Parameter</th>
<th>Estimate* (standard error)</th>
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iiv, inter-individual variability.

FIGURE 1  Schematic representation of best PK plasma model of MPH-IR and MPH-OROS.
ALAC, lag time between administration and onset of absorption; central, central compartment; ka, absorption rate constant; ke, elimination rate constant; i.e., absorption compartment of immediate release methylphenidate; orosIR, absorption compartment of immediate release part of osmotic controlled-release oral-delivery system methylphenidate; orosSR, absorption compartment of sustained release part of osmotic controlled-release oral-delivery system methylphenidate.

FIGURE 2  Goodness of fit plots of the plasma PK model. Upper left: observed (dv) versus population predicted (pred) plasma MPH concentrations (black line is the line of unity); upper right: dv versus individual predicted concentrations (ipre) (black line is the line of unity); lower left: conditional weighted residuals (cwresi) versus pred; lower right: cwresi versus time (time).
FIGURE 3  Individual plasma MPH concentration versus time after administration of MPH-IR (above) or MPH-OROS (under), plotted on a log-linear scale. Dashed lines represent the population prediction, continuous lines represent the individual prediction, and circles represent the observations.
Figure 4: Goodness of fit plots of the saliva PK model. Upper left: observed (dv) versus population predicted (pred) plasma MPH concentrations (black line is the line of unity); upper right: dv versus individual predicted concentrations (ipre) (black line is the line of unity); lower left: conditional weighted residuals (cwresi) versus pred; lower right: cwresi versus time (time).

Figure 5: Pooled distribution of MPH-IR and MPH-OROS cwresi results, visualized as a frequency histogram (left, the line represents a normal distribution), a box plot (middle), and a QQ plot (right).
FIGURE 6  Individual saliva MPH concentration versus time after administration of MPH-IR (above) or MPH-OROS (under), plotted on a log-linear scale. Dashed lines represent the population prediction, continuous lines represent the individual prediction, and circles represent the observations.