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Effect of food and pharmaceutical formulation on desmopressin pharmacokinetics in children

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Abstract

Introduction: Desmopressin is used for nocturnal enuresis treatment in children. In this study, we investigated the pharmacokinetics of two formulations: a tablet and a lyophilisate, in both fasted and fed children.

Methods: Previously published data from two studies (22 children aged 6 to 16 yr and 25 children aged 6 to 13 yr) were analyzed using population pharmacokinetic modeling. A 1-compartment model with first order absorption was fitted to the data. Covariates were selected using a forward selection procedure. The final model was evaluated, and sensitivity analysis was performed to improve future sampling designs. Simulations were subsequently performed to further explore the relative bioavailability of both formulations and the food effect.

Results: The final model described the desmopressin plasma concentrations adequately. Formulation and fed state were included as covariates on the relative bioavailability. The lyophilisate was on average 32.1 % more available than the tablet, and fasted children exhibited an average increase in relative bioavailability of 101%, compared to fed children. Body weight was included as a covariate on distribution volume, using a power function with exponent 0.402. Simulations suggest both the formulation and the food effect are clinically relevant.

Conclusions: Bioequivalence data of two formulations of the same drug in adults, cannot be readily extrapolated to children. This is the first study in children suggesting that the two desmopressin formulations in children are not bioequivalent at the currently approved dose levels. Furthermore, the effect of food intake was found to be clinically relevant. Sampling times for a future study were suggested. This sampling design should result in more informative data and consequently generate a more robust model.

Key points

- Population pharmacokinetic modeling was applied to pediatric desmopressin PK data and used to extract more information out of existing pediatric drug data, generate new information and improve the collection of future information.
- In this study it was found that the established bioequivalence of desmopressin in adults might be different in the pediatric population. A profound food effect was also quantified.
- In order to make solid conclusions regarding desmopressin efficacy in children, PK and PD data should be gathered simultaneously in a well-designed study, for which some design suggestions are presented in this paper.

Abbreviations

AIC Akaike's Information Criterion

AUC area under the plasma concentration-time curve

BCa bias-corrected bootstrap with acceleration constant

CI confidence interval

C_{max} maximum drug concentration

CN condition number

CTS Clinical Trial Simulation

DDAVP Desmopressin

EI Elasticity Index

FIM Fisher Information Matrix

IIV interindividual variability

LSA Local Sensitivity Analysis

MNE monosymptomatic nocturnal enuresis

NPDE normalized prediction distribution error

NPC numerical predictive check

OED Optimal Experimental Design

OFV Objective Function Value

PD pharmacodynamics

PK pharmacokinetics

PopPK population pharmacokinetics

PSN Perl-Speaks-Nonmem

RSE relative standard error

VPC Visual Predictive Check

I. Introduction

Off-label use of drugs in the pediatric population is widespread: 50-90% of prescriptions in pediatrics are off-label and/or unlicensed [1]. The project SAFE-PEDRUG (http://safepedrug.eu) aims to reinvent the strategy for pediatric drug research using a rational combination of bottom-up and top-down approaches, starting from pediatric specificities and opportunities. Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), one of the drugs under study, is a synthetic vasopressin analogue acting on the V2 -receptors located in the collecting ducts of the kidney. It has been applied clinically for more than 30 years, using a range of different formulations: intranasal solution (since 1972), injectable solution (since 1981), tablets (since 1987), and most recently, an oral lyophilisate (since 2005) [2].

Initially, DDAVP was developed to treat adult patients with central diabetes insipidus. Following the observation by Rittig et al., that children with enuresis showed a significantly lower nocturnal increase in arginine-vasopressine (AVP) [3], it was subsequently used for an indication primarily seen in children; enuresis nocturna. Until now, DDAVP is the only drug therapy with evidence level 1, grade A recommendation, for the indication of monosymptomatic nocturnal enuresis (MNE) [4]. Reported adverse events are generally described as mild, and include headache, abdominal pain, nausea, and - typically for the nasal spray [5] - nasal epistaxis, and congestion/rhinitis. Hyponatremia remains an infrequent but very serious adverse event associated with the antidiuretic effect of DDAVP treatment [6]. It has been reported after intake of DDAVP with simultaneous excess intake of fluids [7, 8]. In 2007, the US Food and Drug Administration requested an update of the summary of product characteristics for DDAVP nasal spray following increasing reports on hyponatremia [7], [9]. Since then, the DDAVP spray is no longer indicated for the treatment of MNE, or in patients at risk for hyponatremia in the USA and most European countries [9].

Currently, two oral formulations of DDAVP are labeled for the indication of MNE: a tablet (TAB) and a lyophilisate (MELT). Their bioequivalence at dose strengths of 200 µg and 120 µg, respectively, has been established in adults [10, 11] but not in children. In a previous study, the lyophilisate has been shown to have a superior effect on diuresis in children, which was hypothesized to arise from a less pronounced food interaction [12]. DDAVP is to be taken in a fasted state before bedtime, which is challenging in young children, due to the short time between the last meal in the evening and bedtime. This suggests that the food effect on DDAVP PK/PD should be investigated more thoroughly, as this effect has been established before in

adults [13] but not in children. A published pilot study from our group investigated the PK of both the tablet and lyophilisate formulation in children whom were fed a standard meal [14]. However, only an influence of the formulation on the variability in PK was detected and no fasted control group was included in the analysis. Additionally, suggestions of a body-size effect were found. Given these results, it was decided to set up a new study using a more elaborate sampling scheme to investigate these effects more thoroughly. This paper describes a model-based analysis we set up to increase the efficiency of this future trial.

The purpose of this analysis was two-fold:

1. By pooling previously published pediatric data on DDAVP PK and using a population pharmacokinetics (PopPK) approach, a more in-depth understanding of the effect of formulation, concomitant food intake and patient size on DDAVP PK could be obtained.

2. The developed model was subsequently used to formulate experimental design strategies for the follow-up clinical trial, so that the analysis objectives could be reached as efficiently as possible.

II. Materials and Methods

I. Study data

Only two studies on orally formulated DDAVP PK in children have been published [14], [15], both of which are included in the current analysis. Østerberg et al. compared the PK of an oral lyophilisate in 72 children with MNE to the PK in 28 healthy, adult volunteers using a double-blind, randomized, parallel group, multi-center study [15]. Data from 25 of these children were available for the current analysis. In a second study, De Bruyne et al. used a two-period crossover design to compare the oral lyophilisate to a tablet formulation in children with MNE. Of the 23 children that were included, 22 successfully completed the study, of which the data were available for the current analysis [14]. The 2 datasets are compared in Table 1.

Table 1: Characteristics of the Østerberg and the De Bruyne datasets [14-15].

	Østerberg et al.	De Bruyne et al.
n patients	25	22

Age (years) (median [min-max])	9.7 [6.7 - 13]	12.5 [7 - 16]
Weight (kg) (median [min-max])	32 [25 - 63]	51 [24 - 82]
Sex	5F and 20M	4F and 18M
Height (cm) (median [min-max])	138 [121 - 165]	162 [115 - 186]
Formulation	Lyophilisate	Lyophilisate and tablet
Dose (µg)	0 - 480	200 (tablet) 120 (lyophilisate)
Fed state	Fasted	Fed (standardized 510 kcal meal)
Average n samples per patient	1.9	3 per formulation
Sampling times	0 - 24 h	1, 2 and 6 h
Analytical method	Radioimmunoassay	LC-MS/MS
Linear range	0.8 - 100 pg mL-1	2.00 - 100 pg mL-1

II. Model development

A 1-compartment model with first-order absorption was chosen as a starting point. The log-transform-both-sides (LTBS) approach was used, meaning that the logarithm of the plasma concentrations was modelled. The development of the population model proceeded iteratively, and the inter-individual variability (IIV) was assumed to follow a log-normal distribution. A proportional residual error model (= additive error model in the log domain) was used throughout the entire process. Once an appropriate mixed effects model was obtained, covariate relationships were investigated using a forward selection, adding them to the model one at a time and selecting the models with the best performance metrics to proceed with. The covariates that were tested, were: formulation (MELT), fed state (FED), age (AGE), body weight (WT), sex (SEX), and Tanner Index (TAN).

The decision to include or exclude certain model components was guided by several performance metrics: the Objective Function Value (OFV), Akaike's Information Criterion (AIC), the condition number (CN), and the relative standard error (RSE) of the parameter estimates, obtained through the covariance step in NONMEM. A drop in OFV of 3.84 was assumed to indicate a significantly better fit. Both the OFV and the AIC are based on likelihood ratio tests, that cannot be reliably used to guide in-/exclusion of IIV parameters, especially for sparse data [16]. Thus, for those parameters, decisions were made based on RSE and CN (both should be as low as possible), and standard goodness of fit plots (plots of the observed concentrations versus population- and individual-predicted concentrations, and plots of the residuals).

III. Model evaluation

In order to establish confidence in the final model, different evaluation techniques were applied. A visual and numerical predictive check (VPC and NPC) were performed, without binning or calculating confidence intervals (CIs) on the (sparse) data. Individual and population predictions versus observations plots were also used, and bootstrap analysis was performed. For the latter analysis, 1000 datasets of 47 subjects were resampled with replacement from the original dataset. The bias-corrected bootstrap with acceleration constant (BCa) method was used in order to obtain second-order correct 90% CIs around the parameter estimates [17]. This method corrects for bias and skewness in the standard bootstrap CIs and thus provides a more reliable estimate of the parameter CIs.

The last evaluation technique consisted of normalized prediction distribution error (NPDE) analysis. For this method, the final model was simulated 1000 times using the same design as the original dataset, after which the NPDEs were obtained using the table step in NONMEM [18,19]. Under the null hypothesis that the model describes the data, the distribution of NPDEs should be equal to the standard normal distribution N(0,1).

This hypothesis was formally tested using the Wilcoxon signed-rank test ($H_0 : \mu = 0$), the Fisher variance ratio test ($H_0 : \sigma^2 = 1$), and the Shapiro-Wilks normality test ($H_0 : Z \sim N(\mu, \sigma^2)$).

IV. Sensitivity analysis and sampling design

Sensitivity analysis was performed on the final model. This means, in the broadest sense, that the influence of the different model inputs on the output was studied in a quantitative way. The results can point to parameters that can be excluded (model reduction) or errors in model structure. Furthermore, these results show at which point in time the model output is the most sensitive to an input, and thus when the most information can be gained from an experiment. Therefore, this technique can be used to perform Optimal Experimental Design (OED). In general, two kinds of sensitivity analysis exist: local and global sensitivity analysis [24–26], of which the former was performed in this study.

In this Local Sensitivity Analysis (LSA), the influence of the model parameters was examined in a small window around the nominal (estimated) value. Because of this small perturbation, the change in response can be described by a first order approximation, and the sensitivity of the

output to each input can be calculated using the partial derivative of that output to each specific parameter.

In order to be able to compare these sensitivities, they were normalized to Elasticity Indices (EIs), which have the same units (pg ml^{-1}) as the output (see equation 1). These EIs can be compared between different parameters, independent of the parameter values.

$$EI_{y\ to\ \theta_i} = \frac{\partial y(\Theta)}{\partial \theta_i} * \theta_i$$

Equation 1: Elasticity Indices

The results of the LSA were compared to an OED performed using PopED for R [18]. In this design, optimal sampling times were calculated based on optimization of the population Fisher Information Matrix (FIM) [25], which should result in more efficient designs than the use of a LSA on its own. Five iterations of a sequence of random search (300 iterations), stochastic gradient (150 iterations) and linear search (step size = 40) algorithms were used to identify the optimal design.

V. Simulation-based analysis

Once confidence in the model had been achieved during the evaluation step, it was used for simulation. On the one hand, the established average bioequivalence of 120 µg lyophilisate and 200 µg tablet [10], [11], and the food effect [13] previously reported in adults were further analyzed for their clinical relevance in this pediatric dataset. On the other hand, the optimal sampling times found before were applied in a sample size calculation for a bioequivalence trial.

To investigate the effect of the 2 DDAVP formulations and of the food intake, clinical trial simulations (CTSs) were performed. For this, 20 patients were sampled randomly (by body weight, as no other covariates were present in the final model) from a lognormal body weight distribution for children aged 7 to 16 year [23]. These 20 patients then were simulated to undergo 4 scenarios: administration of 120 µg lyophilisate while fed (MELT + FED), 200 µg tablet while fed (TAB + FED), 120 µg lyophilisate while fasted (MELT + FAST) and 200 µg tablet while fasted patients (TAB + FAST). For each scenario and patient, the area under the plasma concentration-time curve ($AUC_{0-\infty}$) and maximum drug concentration (C_{max}), and their logarithms were calculated from 8 simulated samples, taken at the optimal times determined

by the LSA. As is recommended by the FDA [24], an additional sample at 24h was included in this design, to minimize extrapolation in the AUC calculation.

For each trial of each individual, the following ratios were calculated to separate the formulation and the food effect:

$$Formulation\ effect:$$

$$\Delta \log(AUC_A) = \log(\frac{AUC_{TAB,A}}{AUC_{MELT,A}})$$

$$\Delta \log(C_{max,A}) = \log(\frac{C_{max,TAB,A}}{C_{max,MELT,A}})$$

$$Food\ effect:$$

$$\Delta \log(AUC_B) = \log(\frac{AUC_{B,FAST}}{AUC_{B,FED}})$$

$$\Delta \log(C_{max,B}) = \log(\frac{C_{max,B,FAST}}{C_{max,B,FED}})$$

Where A = FED or FAST and B = TAB or MELT. Two formulations are considered bioequivalent when the 90% CIs of the geometric mean of their AUC- and C_{max} -ratios fall between 80% and 125% [20, 21]. As these means are equal to the log-average, the CIs on the log-ratios were calculated using the modified Cox method (equation 2, [27]) which were subsequently exponentiated to obtain the normal CI.

$$CI = \exp(\hat{Y} + \frac{\sigma^2}{2} \pm \sqrt{\frac{\sigma^2}{n} + \frac{\sigma^4}{2(n-1)}})$$

Equation 2: Modified Cox method

Where $\hat{Y}$ is the mean of the log-ratios, σ is the standard deviation, n is the sample size (20), and t is the 90% value of the two-sided t-distribution with n − 1 degrees of freedom (≈ 1.33 for n = 20). The CIs for the food effect were calculated and interpreted in the same way, as is recommended by the FDA [28], resulting in the acceptance or rejection of bioequivalence and food effect for that particular trial. These trials were repeated 1000 times and the resulting CIs were then summarized by taking the median of the lower, upper and mean values. Furthermore, the percentage trials which resulted in acceptance of bioequivalence were calculated. Eventually, a sample size calculation for a crossover two-period bioequivalence study with doses suggested by the

estimated model parameters was performed, both in fed and fasted patients. This sample size calculation took parameter uncertainty into account by sampling each parameter from a multivariate normal distribution based on the variance-covariance matrix, resulting in 1000 parameter sets for each number of individuals.

VI. Software

Model development and parameter estimation were performed using NONMEM v. 7.3 [29], with FOCE as estimation algorithm, accessed with the software Perl-Speaks-Nonmem (PSN) [30], embedded in the workbench Piraña [31]. RStudio (v. 0.98, http://www.rstudio.com/) was used to prepare the datasets, perform the simulations, and post-process all results, which included the statistical calculations and plot generation. The LSA was performed using the biointense model environment in Python. This package is "an object oriented python implementation for model building and analysis, focusing on sensitivity and identifiability analysis" [32]. It was accessed using Spyder v. 2.3.3 [33].

III. Results

I. Model development

The model development path is depicted in Table 2. The available data was used to its limits, as not all random effects could be estimated without inflating the condition number. This is caused by the sparseness of the data. After model 29 was run (the final model), other covariates (age, tanner index, BMI and sex) were tested on all the fixed effects. Different relations (E_{max}, sigmoidal, exponential and allometric scaling) were also tested for these covariates. None of them improved the model significantly and often a significant increase in OFV was found instead (data not shown). Therefore, model 29 was chosen as the final model. The final model structure and parameters are found in Table 3.

Table 2: Model development path to the final model

Run #	Ref #	OFV	ΔOFV	AIC	CN	Max(RSE)	Description
1		-4.482		5.518			One compartmental model with first order absorption. Estimation of fixed effects.
7	1	-32.237	-27.755	-20.237	34	35%	Estimation of IIV on F_1 + fixed effects.
11	1	-4.482	0	3.518			Fix F_1 (no IV data) to 1.
15	11	-32.237	-27.755	-22.237	17	35%	Estimation of IIV on F_1 + fixed effects.
17	15	-35.976	-3.739	-23.976	34	77%	Estimation of IIV on F_1 and V_d + fixed effects.
21	11	-49.413	-44.931	-37.413			Addition of formulation effect covariate to model before estimating IIVs, estimate fixed effects and IIV on formulation effect.
23	21	-70.275	-20.862	-56.275	32	36%	Estimation of IIV on formulation effect and V_d + fixed effects.
27	23	-85.594	-15.319	-69.594	84	56%	Addition of food effect covariate to model before estimating IIV on formulation effect and V_d + fixed effects.
28	27	-83.954	1.64	-67.954	84	47%	Put IIV on F1 (lumped) instead of on formulation effect.
29	**28**	**-87.758**	**-3.804**	**-69.758**	**40**	**46%**	**Addition of body weight as a covariate to V_d using a power function (Final Model).**

Fig. 1: VPC for the different scenarios present in the data. The line represents the median model prediction for each scenario, the grey area represents the 90% prediction interval.

Fig. 2: VPC for all data pooled together. The line represents the total median model prediction, the grey area represents the 90% prediction interval.

Fig. 3: Population and individual predictions versus observed concentrations. The dotted line represents the unity line and the full line represents a Loess smoother through the data points.

Fig. 4: NPDE distribution (left) and QQ-plot (right). $\mu = 0.00569$, $\sigma = 1.01$.

II. Model evaluation

In Figure 1, VPCs for the three different scenarios present in the data (MELT + FAST, MELT + FED, and TAB + FED) are shown. The model seems to perform best for patients who receive the lyophilisate formulation. The numerical predictive check was performed on the full VPC (Figure 2). 2.80% of the observations lay above the 90% PI and 3.50% of the observations lay below the 90% PI, indicating good model performance. Figure 3 shows the population and individual predictions plotted against the observations: no significant deviations from the line of unity are seen.

The 90% CIs of the BCa bootstrap analysis (818/1000 runs completed minimization) are included in Table 3. The bootstrap estimates deviated between −7.53% and +4.50% from the model estimates, with an average deviation of 0.21%. Bootstrap-estimated relative standard errors (between 18.2% and 84.9%) were consistently higher than the standard errors estimated in NONMEM (between 10% and 46%).

The NPDE results are shown in Figure 4. No significant deviations from the standard normal distribution could be detected, as is shown in Table 4.

Table 3: Population pharmacokinetic model parameter estimates and bootstrap values.

Parameter	**Estimate [%RSE]**	**Bootstrap** [90%CI]
$CL/F = \vartheta_1 * e^{\eta_1}$	4982 L/h [12%]	4964 [4002 – 5820]
$V_d/F = \vartheta_2 * (WT/45.5)^{\vartheta_7} * e^{\eta_7}$	23346 L [13%]	23345 [17817 – 28366]
$k_a = \vartheta_3 * e^{\eta_3}$	1.65 h^{-1} [25%]	1.72 [1.01 – 2.58]

$F = (\vartheta_4 + \vartheta_5 * \text{MELT} + \vartheta_6 * \text{FASTED}) * e^{\eta_4})$	1 FIX	1 FIX
Influence of MELT (ϑ_5)	0.321 [46%]	0.333 [0.0486 – 0.548]
Influence of fasted state (ϑ_6)	1.01 [25%]	1.05 [0.579 – 1.45]
Influence of weight (ϑ_7)	0.402 [44%]	0.397 [0.118 – 0.731]
IIV on CL	0 FIX	0 FIX
IIV on V_1	27.3%[2] [15%] (39% Shrinkage)	25.2% [16.5% – 46.0%]
IIV on k_a	0 FIX	0 FIX
IIV on F_1	21.1% [10%] (39% Shrinkage)	21.1% [11.6% – 31.2%]
Proportional residual error	38.5 CV% [14%]	37.8 CV% [34.4% – 44.1%]

Table 4: Formal tests for H_0 : NPDE-distribution = N(0, 1)

Test	H_0	**Value**	**p-value**	**Conclusion**
Wilcoxon signed-rank	$\mu = 0$	V = 5153	0.994	H_0 cannot be rejected
Fisher variance ratio	$\sigma^2 = 0$	F = 1.03	0.770	H_0 cannot be rejected
Shapiro-Wilks	Z ~N(μ, σ^2)	W = 0.989	0.315	H_0 cannot be rejected

[2] Coefficient of variation, calculated as $CV\% = 100\% * \sqrt{e^{\omega} - 1}$

III. Sensitivity analysis and sampling design

The calculated EIs versus time are presented in Figure 5. Sensitivity function optima are marked with green stars. These optima are considered good sampling time points, as the output is the most sensitive to a certain parameter at those points, enabling optimal estimation of this parameter [22], [34]. The most important parameters (i.e. the one with the largest area under the sensitivity function) are the relative bioavailability and dose, the effect of food intake, V_d, and CL.

Based on this analysis, sample times for a subsequent clinical study with rich sampling were suggested. Intensive sampling of the absorption part (< 3 h) is needed to capture all information present during this part of the PK profile. The elimination phase is much less informative and should not be sampled equally intensive. The proposed sampling scheme for a study with 8 time points was 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 5 h and 6 h.

The results of the FIM-based OED are shown in Figure 6. The resulting sampling scheme for 8 time points is presented in Table 5. The optimal design was 1.34 times more efficient than the initial (LSA-derived) design. Merging of optimal times close to each other resulted in minimal loss of efficiency. This reduced design was 1.22 times more efficient than the initial LSA-derived design.

Table 5: Optimal experimental design

Scenario	**Sample times (h)**							
MELT + FED	0.475	0.8	0.8	2.15	2.375	4.4	5.5	5.8
MELT + FASTED	0.3259	0.475	0.8	1.85	2.075	5.8	5.8	5.8
TAB + FED	0.4	0.65	0.8	2.025	2.15	6.1	7.2	7.2
TAB + FASTED	0.525	0.525	0.8	1.735	2.053	4	6.85	7.8

Fig. 5: Relative sensitivity of the predicted DDAVP plasma concentrations to the model parameters. The blue pentagons refer to original sample times [8], whereas the green stars represent proposed optimal sampling times.

Fig. 6: FIM-based optimal sampling design. The profiles are expected population averages for the different scenarios and the circles are suggested sampling times.

IV. Simulation-based exploration

Bioequivalence and food effect

The CTSs are summarized in Figure 7. In none of the simulated trials, the different formulations/ fed states were found to be bioequivalent. The simulations, in Figure 7, show how the food effect is more apparent than the formulation effect. Simulated subjects experience a higher exposure to DDAVP when they are fasted than when they have received a standard meal. In addition, a 200 µg tablet results in a higher exposure compared to a 120 µg lyophilisate while in adults, these dose levels resulted in equivalent exposure. In order to quantify the relevance of these effects, the median 90% CIs for the ratio of geometric means of $AUC_{0-\infty}$ and C_{max} were calculated and are presented below.

Formulation effect:

$$AUC - ratio = 138\% [133\% - 144\%]$$

$$C_{max} - ratio = 144\% [135\% - 153\%]$$

Food effect:

$$AUC - ratio = 194\% [187\% - 201\%]$$

$$C_{max} - ratio = 202\% [190\% - 215\%]$$

When applying EMA and FDA guidelines to the results of this simulation study, a significant food effect is concluded to be present for DDAVP in children [20, 21]. The established bioequivalence of 200 µg tablet and 120 µg lyophilisate is also rejected, based on these simulations. It can thus be expected that in a real trial, bioequivalence between the 200 µg tablet and 120 µg lyophilisate

cannot be claimed. Indeed, a point estimate of 138% suggests that the ratio of dose strengths (120 µg lyophilisate versus 200 µg tablet) is suboptimal and a higher lyophilisate dose is needed to reach similar exposure as compared to the 200 µg tablet. Using the parameter estimate of the formulation effect (0.3208), we calculated that the equivalent dose of lyophilisate to 200 µg tablet is 151.4 µg. At this point, a new CTS was performed using these newly suggested dose strengths. The results are shown in Figure 8 and show an almost complete overlap of the concentration-time profiles for both formulations.

Fig. 7: Simulated DDAVP plasma concentrations for the four different scenarios (120 µg lyophilisate, 200 µg tablet). The lines represent the average response and the colored areas represent the 95% prediction intervals. On the left, the effect of the different formulations is depicted; on the right, the food effect is shown.

Fig. 8: Simulated DDAVP plasma concentrations for the four different scenarios (150 µg lyophilisate, 200 µg tablet).

In order to further support this new dose, a proper two-period cross-over bioequivalence trial should be performed with 150 µg lyophilisate and 200 µg tablet. A power curve was approximated for this design, by simulating this trial 1000 (parameter uncertainty) * 1000 (IIV) times for 1 up to 50 patients and calculating the power as the number of times bioequivalence was proven divided by the total amount of trials (1000). The results for fed patients are shown in Figure 9: approximately 20 patients would be needed for a median power of 80%. Using fasted patients, approximately 250 patients would be needed (results not shown).

Fig. 9: Approximated power curve for a two-period cross-over bioequivalence trial with fed patients. The colored areas represent the 90% prediction interval.

IV. Discussion

In this study, we investigated the pharmacokinetics of desmopressin in a pediatric population. In order to do this, two data sets of previously published clinical trials were combined, enabling the use of the specifics (e.g. food intake or not, sampling schemes,...) of both data sets and thus the extraction of more information from the data. Nonlinear mixed effects modeling was used and a 1-

compartmental model with first order absorption was able to describe the data well. In previous studies, more complex models such as a 2-compartmental model [35], a 3-compartmental model [36] and a 1-compartmental model with transit compartments [15] have been used to describe DDAVP PK. The first two, however, describe DDAVP pharmacokinetics after intravenous dosing, which indeed follow biphasic kinetics [37]. Possibly, this biphasic behavior is masked by the absorption process after oral dosing. A two compartment model was tried but resulted in a significantly worse fit than the one compartment model (ΔOFV = +81.3) The use of a transit model could be argued, as the absorption kinetics of DDAVP do seem to be delayed; the mean residence time and number of compartments in children have been estimated as 0.237 h and 1.19, respectively [15]. The simple first order absorption model was compared with the transit compartment model, but this showed no significant improvement ($\Delta OFV_{transit}$ = +8.502). For reasons of parsimony, the first order absorption model was hence retained.

In our study, a population apparent clearance (CL/F) of 4892 L/h was found. This is almost twice the value found in the pediatric dataset by Österberg et al. [15]. However, in our study we allowed the relative bioavailability to change, depending on the formulation and the fed state. If we calculate the population CL/F for a fasted population receiving the lyophilisate formulation, CL/F becomes 4892/(1+0.3208+1.011) = 2098 L/h, which corresponds with the reported value of 2330 L/h by Österberg et al.[15]. The same reasoning can be followed for the apparent volume of distribution (V_d/F). However, to compare both values correctly, V_d/F should be calculated for the average body weight from the full Österberg dataset (28 kg [15]). V_d/F then becomes $23346*(28/45.5)^{0.4020}$ = 8237 L, which corresponds to the reported value of 8510 L [15].

The bioequivalence between 200 µg tablet and 120 µg lyophilisate found in adults [10], [11], [37] could not be supported by the current analysis. The statistical significance of the formulation effect is apparent from our model, suggesting that the 120 µg lyophilisate is 32.1% more bioavailable than the 200 µg tablet. In adults, this value was found to be (200/120 – 1) = 66.7% for a similar strength lyophilisate and tablet. Indeed, when a lyophilisate dose of 150 µg (33.3% lower than 200 µg) is simulated (Figure 7), the desmopressin exposure of the two formulations in children shows a much better overlap. A possible explanation for this phenomenon could be a reduced sublingual absorption in children, caused by either the lower surface area compared to adults, or the fact that the lyophilisate is swallowed sooner by children. This could be formally tested in a two-period cross-over clinical bioequivalence trial.

The effect of food intake was also found to be clinically significant. Attributing this effect exclusively to food intake might be considered too simplistic, as all fasted patients originated from

the Österberg study and all fed patients originated from the De Bruyne study, which means other factors might confound our analysis. There are two major differences between the studies: the bioanalytical method and the level of hydration. Since the two analytical methods were both validated and had a similar linear range, it seems unlikely that this has confounded our estimate for food effect to any significant degree. In the De Bruyne study, hydration was maintained by oral water administration, 5 hours after dose. Patients in the Österberg study, however, drank 1.5% of their body weight as water during 30 minutes after which urinary output loss was replaced with an equivalent amount of tap water [14], [15]. Notwithstanding this difference in hydration method, it was previously shown that hydration does not significantly influence the PK of DDAVP [35] and it is thus highly improbable that the difference between the two study groups can be attributed to this. However, between-study-variability might still be present in this effect parameter, as is e.g. indicated by the large difference in power curve for a two-period cross-over bioequivalence study in respectively the fed (20 patients for 80% power) and fasted population (250 patients).

As children are not always fasted when they take DDAVP (right before bedtime), this food effect can have consequences for the optimal dosing. Even though the effect on the maximal response might be negligible, as it is in adults, there might be an influence on the duration of action [13].

An effect of WT on V_d/F was also found, indicating that dose adjustment could be necessary to maximize efficacy in this pediatric population. However, the extent of the body weight influence is quite unclear from these data, as the exponent of the power relation exhibits quite a large uncertainty. More informative trials can result in smaller CIs for this (and other) parameters. Indeed, although model evaluation was positive, the amount of information in the data seems to be exhausted in this (relatively simple) model. This is e.g. clear from the failure to additionaly estimate an IIV on CL and k_a. However, the variability of CL in the population is still somewhat captured by the model, as CL and Vd are apparent clearance and volume of distribution, which are correlated via the bioavailability F. This way, the IIV on CL is partially captured by the IIV on F and Vd. K_a, and especially its IIV, should be estimated though, which is why a new trial with more intensive sampling of the absorption region is needed.

Therefore, a sensitivity analysis was conducted in order to suggest sampling times for a new trial. More intensive sampling in the absorption phase is advisable, as is proposed by both the LSA as well as the OED. We suggest to design the trial according to the LSA results, as these time points are more practical in a clinical setting, and the OED was only 1.34 times more efficient than the LSA-design. This design was based on 8 samples, while theoretically speaking 3 sampling points

(the number of parameters in the model) should be sufficient [34]. However, as the follow-up study will also investigate PD and due to logistical risks, more samples are preferable.

As the difference between two formulations is not only a matter of PK, PD will also be monitored in this new trial. It was e.g. demonstrated in adults that there is a significant effect of sex on the DDAVP PD [38]. This effect is thought to be caused by a difference in V2-receptor expression [39] and should also be investigated in children. As our study is based exclusively on PK data, no inferences about the optimal sampling scheme for PD analysis could be made. In the newly designed trial, PD characteristics such as urine volume and plasma osmolality will be measured after which a population approach will be used to gain knowledge about the complete PK/PD behavior of DDAVP in the pediatric population.

In conclusion, in this analysis we have presented evidence for an effect of body weight and fed state on the pharmacokinetics of desmopressin in children. Furthermore, the relative bioavailability between the lyophilisate and tablet formulations is probably not the same in children as in adults. We should be reluctant to accept bioequivalence in children based on adult data alone. Our study also offers suggestions for optimizing the sampling design of a new trial and a sample size calculation for a bioequivalence trial was also provided.

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Conflict of interests

An Vermeulen is an employee of Johnson & Johnson and holds stock/stock options from J&J. Pauline De Bruyne received a travel reimbursement from Ferring pharmaceuticals for a presentation at the Ghent-Aarhus Springschool. Johan Vande Walle has received consulting fees and travel reimbursements from Ferring pharmaceuticals and payment for lectures from Ferring pharmaceuticals and Astellas Pharma. Robin Michelet, Lien Dossche, Pieter Colin, Koen Boussery, Jan Van Bocxlaer have no potential conflicts of interest that might be relevant to this manuscript.

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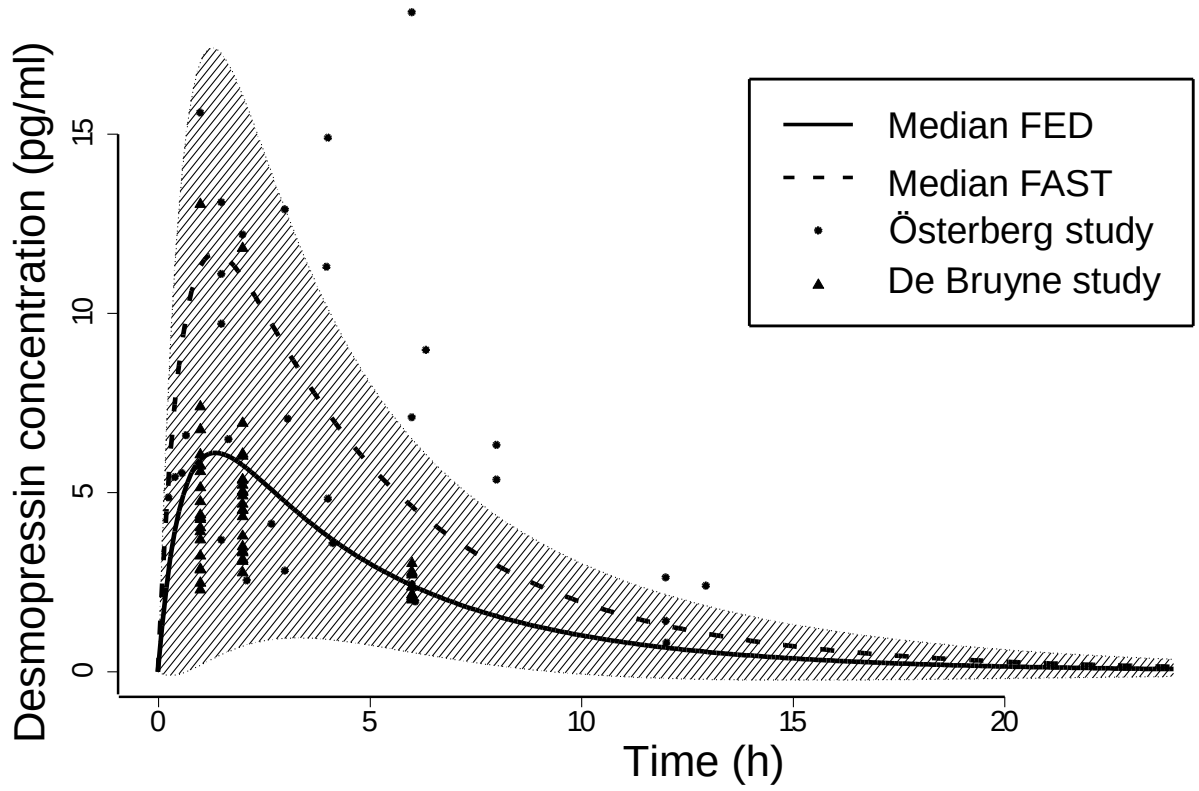
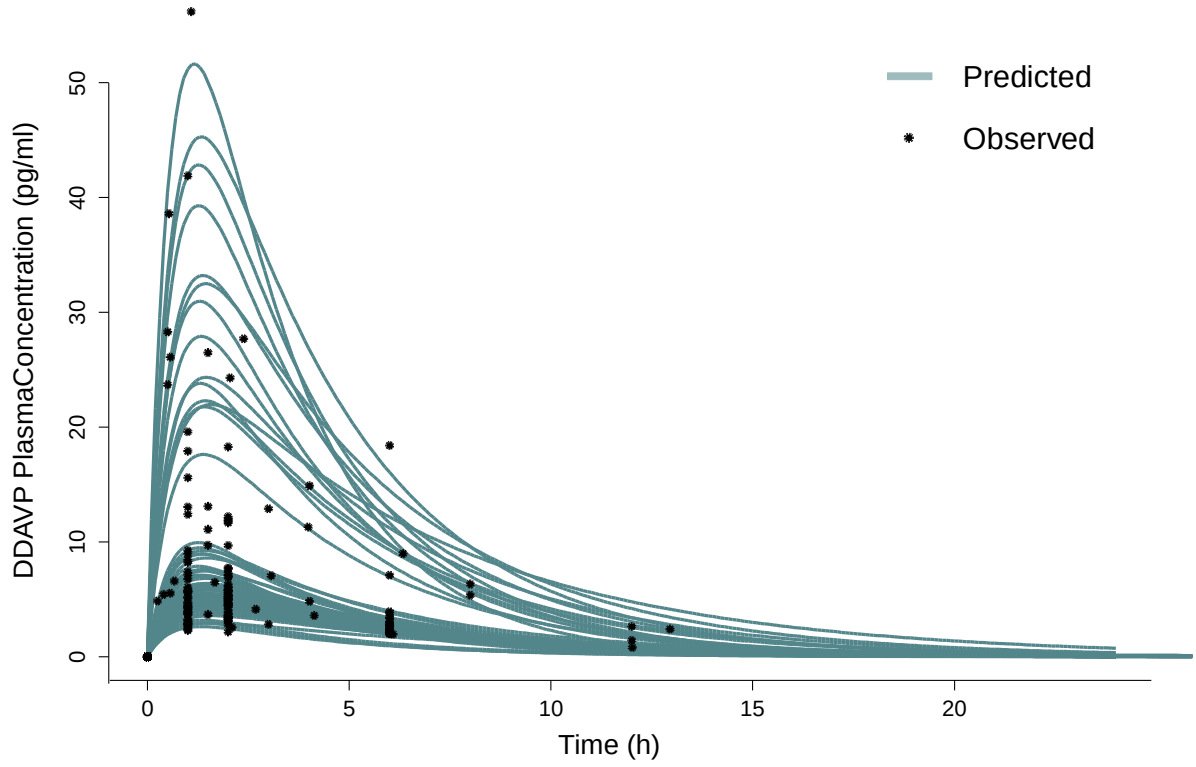


Figure 1



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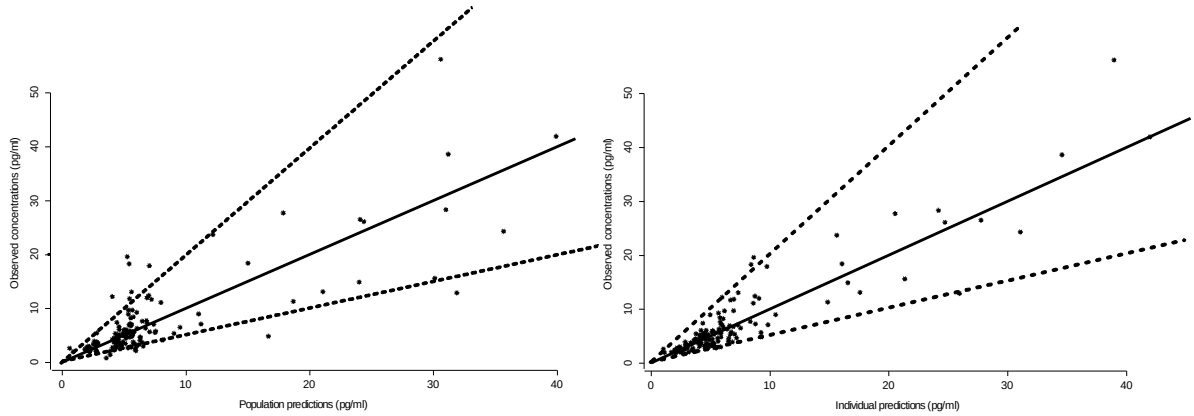
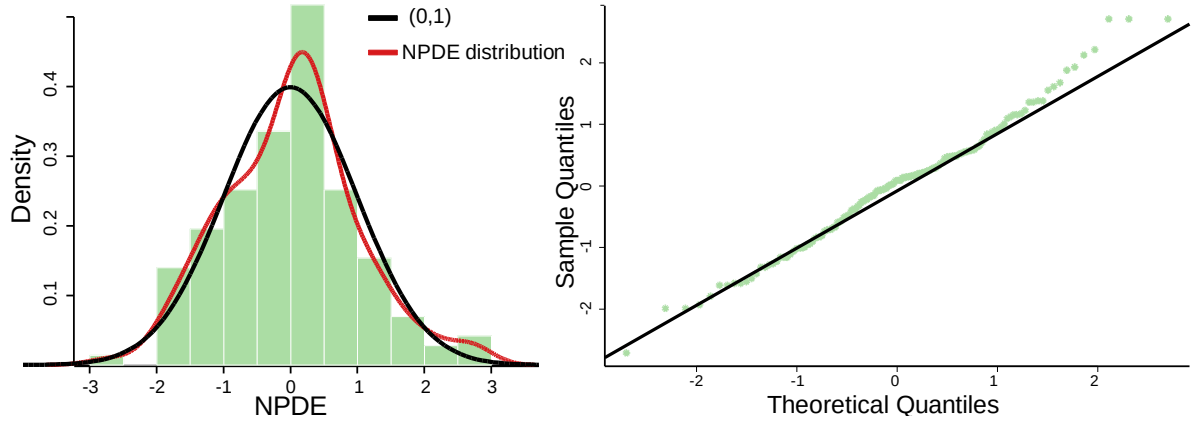


Figure 3



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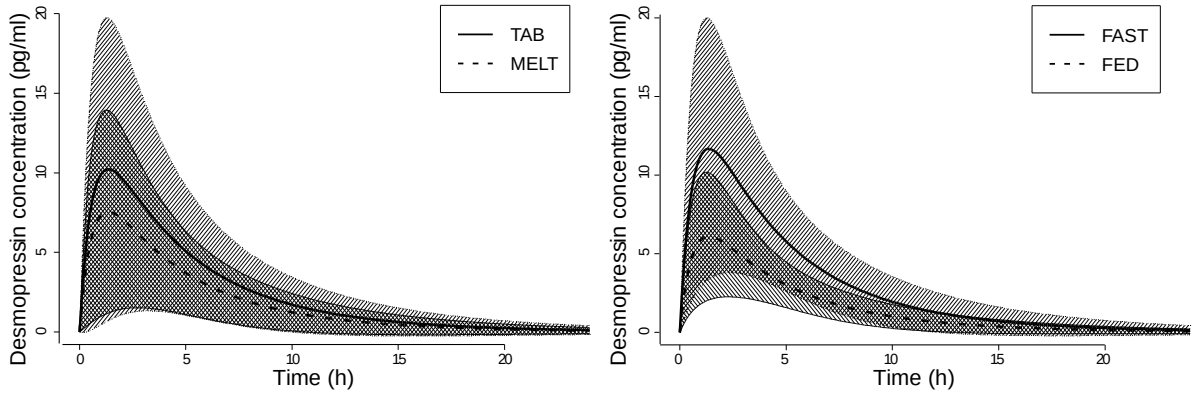

Figure 5

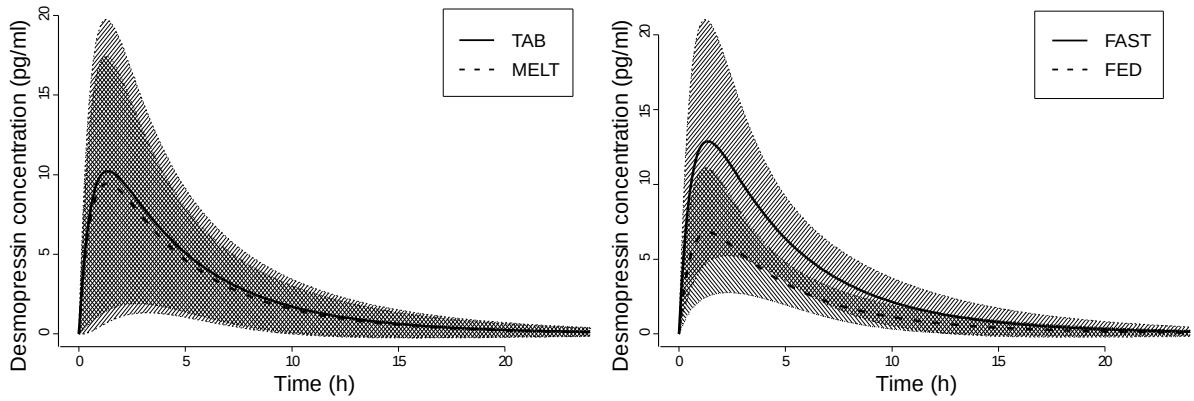

Figure 6

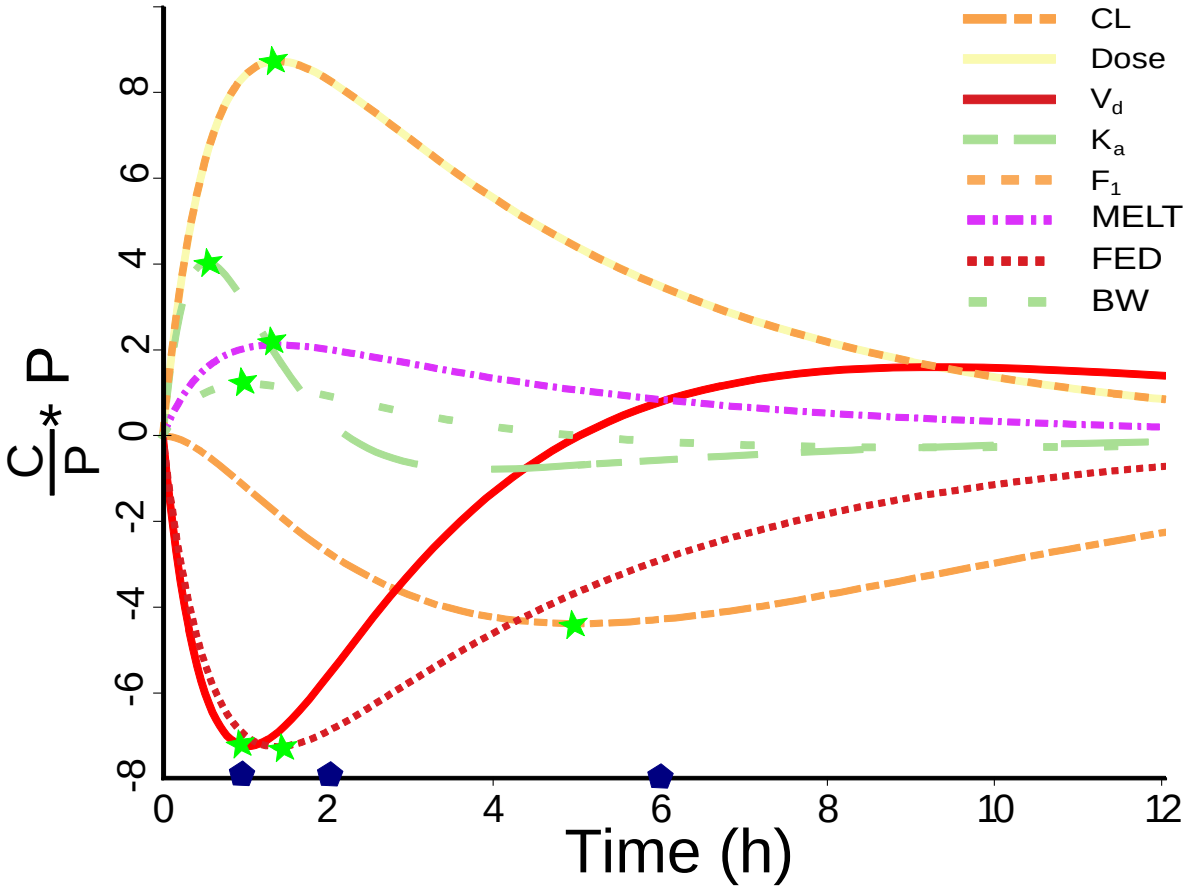

Figure 7

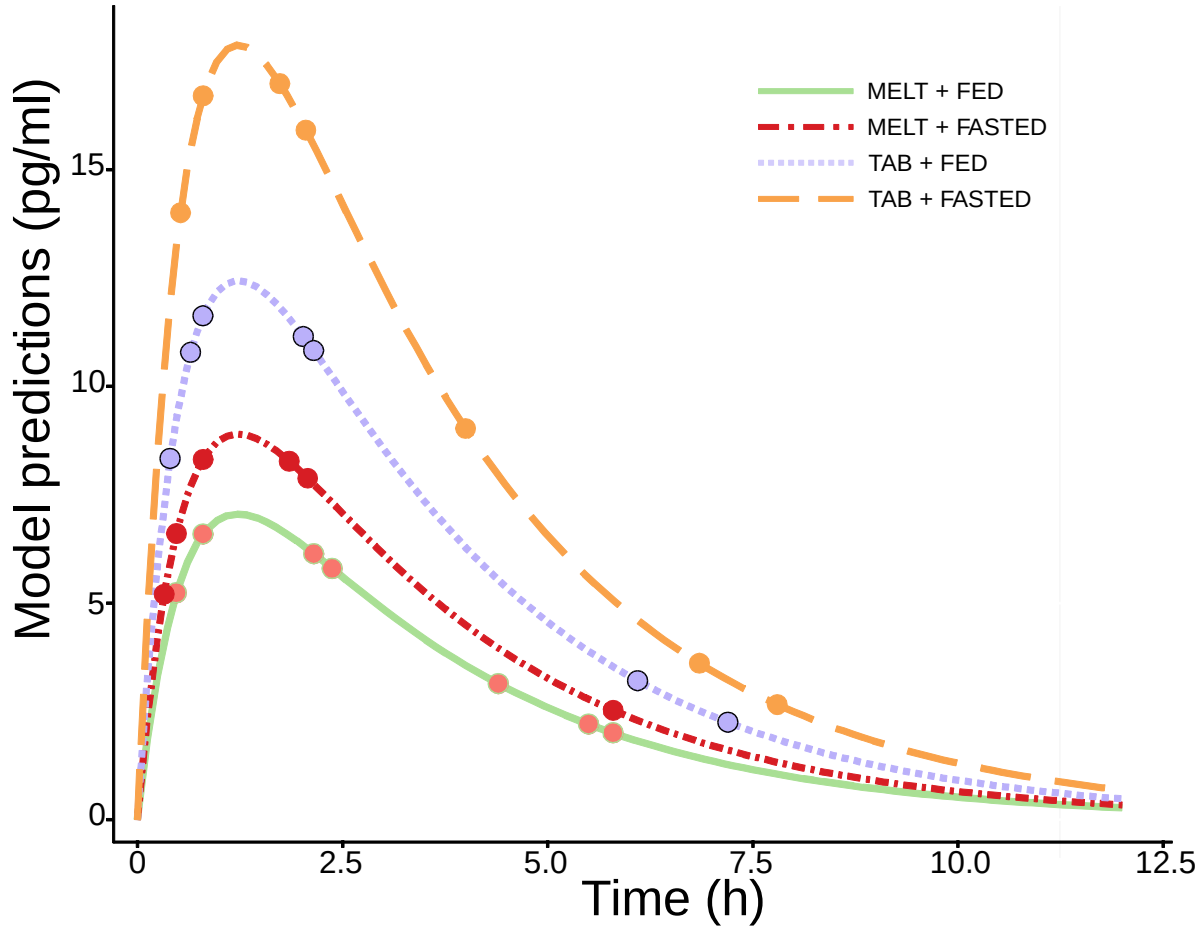
Model predictions (pg/ml)
0
5
10
15
0
2.5
5.0
7.5
10.0
12.5
Time (h)
MELT + FED
MELT + FASTED
TAB + FED
TAB + FASTED

Figure 8