

Bioequivalence of desmopressin in children

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Introduction

Desmopressin (DDAVP) is a synthetic vasopressin analogue used in nocturnal enuresis treatment. Two formulations, a tablet (TAB) and a lyophilisate (MELT), exist of which the bio-equivalence has been established in adults but not in children. This study analyzes two clinical trials to investigate how the drug product and intake of food influence DDAVP pharmacokinetics in children and provides suggestions for subsequent studies.

Methods

Patient data

De Bruyne [1]	Österberg [2]
n = 22	n = 28
age = 12.7 y	age = 10.5 y
WT = 50.1 kg	WT = 40.9 kg
200 µg TAB	No TAB
120 µg MELT	0 – 480 µg MELT
3 samples pp	1.9 samples pp
Fed	Fasted

Model

A 1-compartment model with first order absorption was fitted to the data using NONMEM (v.7.3 [3]). Covariates were selected through one-by-one screening to construct a full model, followed by backwards deletion. The final model *goodness-of-fit* was evaluated by means of bootstrapping and NPDE-analysis, and a *sensitivity analysis* (SA) was performed to investigate the sampling design.

Conclusion

For the first time in children, the food effect on DDAVP pharmacokinetics was proven to be significant. 120 µg MELT and 200 µg TAB don't seem to be bioequivalent. For further studies, sampling times were suggested, which should result in more informative data.

References

- [1] De Bruyne, P., De Guchteneere, A., Van Herzele, C., Raes, A., Dehoorne, J., Hoebeker, P., Van Laecke, E., and Vande Walle, J. *European journal of pediatrics* 173(2), 223–8 February (2014).
- [2] Osterberg, O., Savic, R. M., Karlsson, M. O., Simonsson, U. S. H., Nørgaard, J. P., Vande Walle, J., and Agersø, H. *Journal of clinical pharmacology* 46(10), 1204–11 October (2006).
- [3] Boeckmann, A. J., Sheiner, L. B., and Beal, S. L. (2006).
- [4] Rittig, S., Jensen, A. R., Jensen, K. T., and Pedersen, E. B. *Clinical Endocrinology* 48, 235–241 (1998).

Results

Three covariates were identified: body weight (on V_d), formulation (on F_1) and study effect (also on F_1). As the only difference between the studies was the administration of food, the study effect was assumed to be an indicator of the food effect. This food effect was demonstrated in adults ([4]) and is thus expected to be present in children as well. The parameter values, along with the estimated bootstrap values (818/1000 runs successful) are presented in table 1.

Table 1: Population pharmacokinetic model parameter estimates and bootstrap values

Parameters	Estimate [%RSE]	Bootstrap [90%CI]
θ_1 ($CL/F = \theta_1 * e^{\eta_1}$)	4892 [12%]	4961 [4104 – 5973]
θ_2 ($V_1/F = \theta_2 * \frac{WT^{\theta_7}}{45.5} * e^{\eta_2}$)	23346 [13%]	23550 [17860 – 28410]
θ_3 ($k_a = \theta_3 * e^{\eta_3}$)	1.646 [25%]	1.720 [0.9920 – 2.554]
θ_4 ($F_1 = (\theta_4 + \theta_5 * MELT + \theta_6 * FASTED) * e^{\eta_4}$)	1 FIX	1 FIX
θ_5 Influence of formulation	0.3208 [46%]	0.3329 [0.0897 – 0.5890]
θ_6 Influence of food intake	1.011 [25%]	1.050 [0.6196 – 1.516]
θ_7 Influence of weight	0.4020 [44%]	0.3974 [0.1023 – 0.7178]
ω_1 IIV on CL	0 FIX	0 FIX
ω_2 IIV on V_1	26.84% [15%]	24.95% [8.05% – 36.220%]
ω_3 IIV on k_a	0 FIX	0 FIX
ω_4 IIV on F_1	20.89% [10%]	20.94% [10.34% – 29.58%]
σ Proportional residual error	0.1385 [14%]	0.1338 [0.1022 – 0.1659]

To increase confidence in the model, the distribution of the normalized prediction distribution errors (NPDE) was examined, as shown in figure 1. Non-normality could not be detected using the Shapiro-Wilk test and the model was thus found to describe the data well.

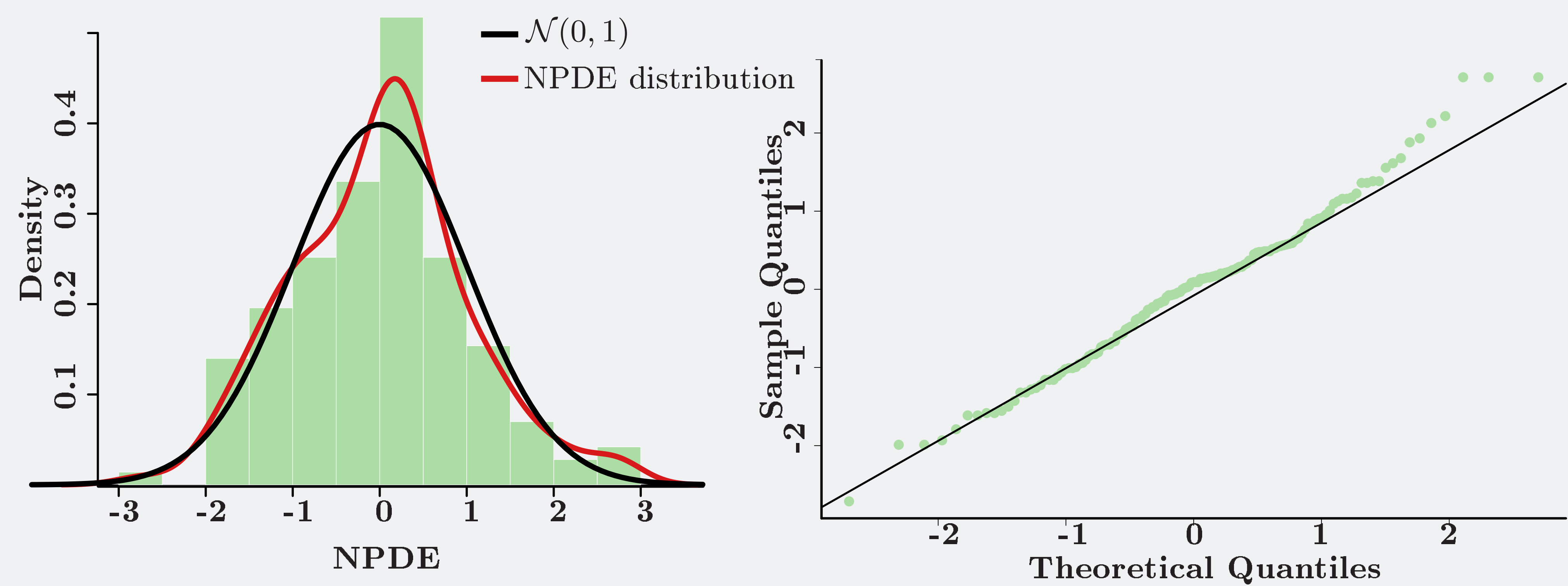


Figure 1: NPDE result. $\mu = 0.005687818$, $\sigma = 1.008649$, Shapiro-Wilk = 0.989, $p = 0.318$

Sensitivity Analysis

Being confident in the model, a sensitivity analysis was performed to determine optimal sampling points. As is depicted in figure 2, where the elasticity indices are plotted, the plasma concentrations are most sensitive to the model parameters in the early post-dosing phase. It is thus recommended to sample frequently in the time between 15 minutes and 2 hours post-dose. The period after six hours is also interesting to sample as the plasma concentrations are only sensitive to the clearance parameter then.

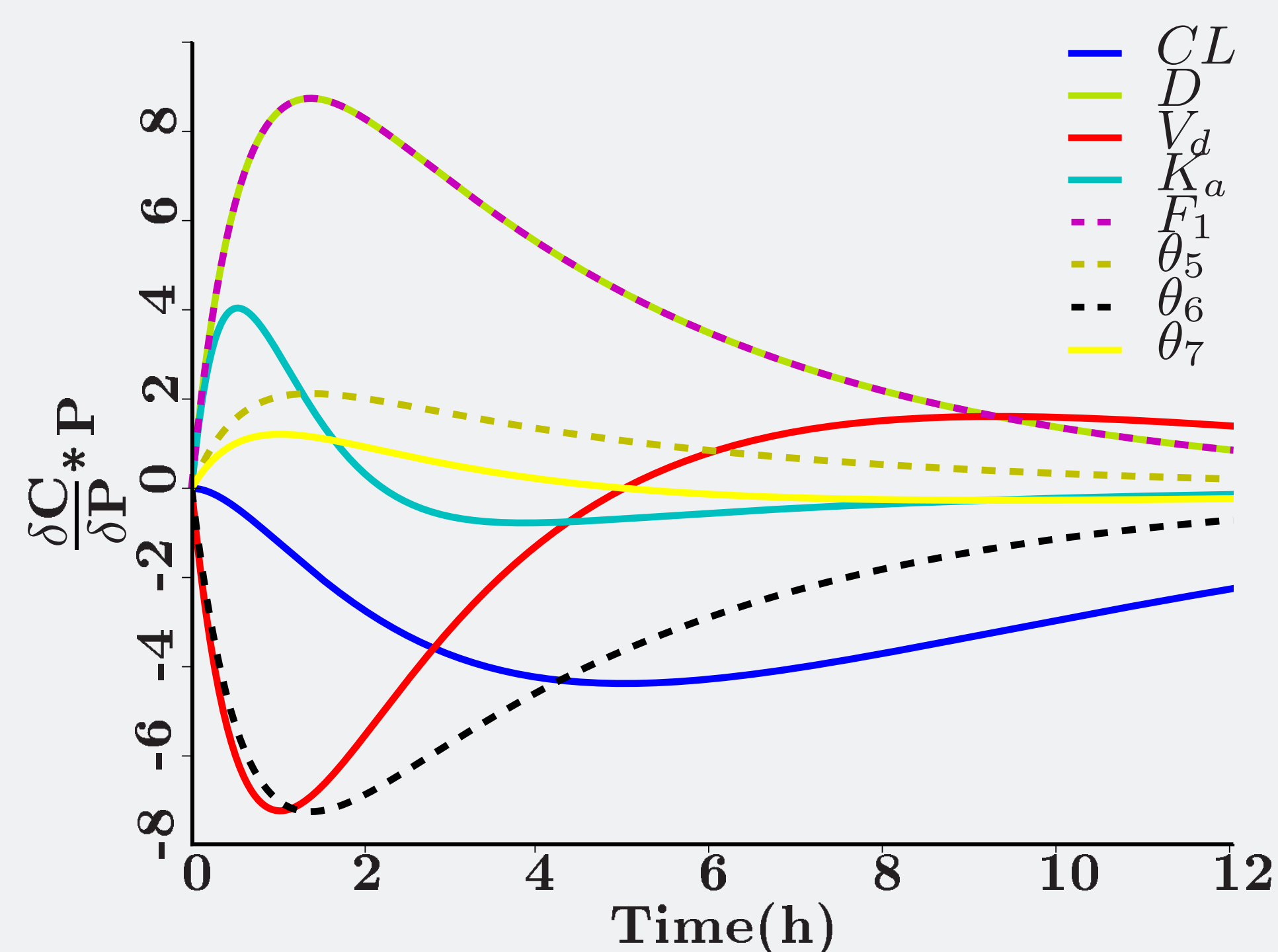


Figure 2: Sensitivity of DDAVP plasma concentrations to model parameters

Bioequivalence and food effect

Four scenarios (Fed, Fasted, MELT and TAB) were simulated using the 50 patients (figure 3, 10 simulations per patient per scenario). The 90% CI for the geometric mean of the ratio of AUC and C_{max} were calculated and are presented below.

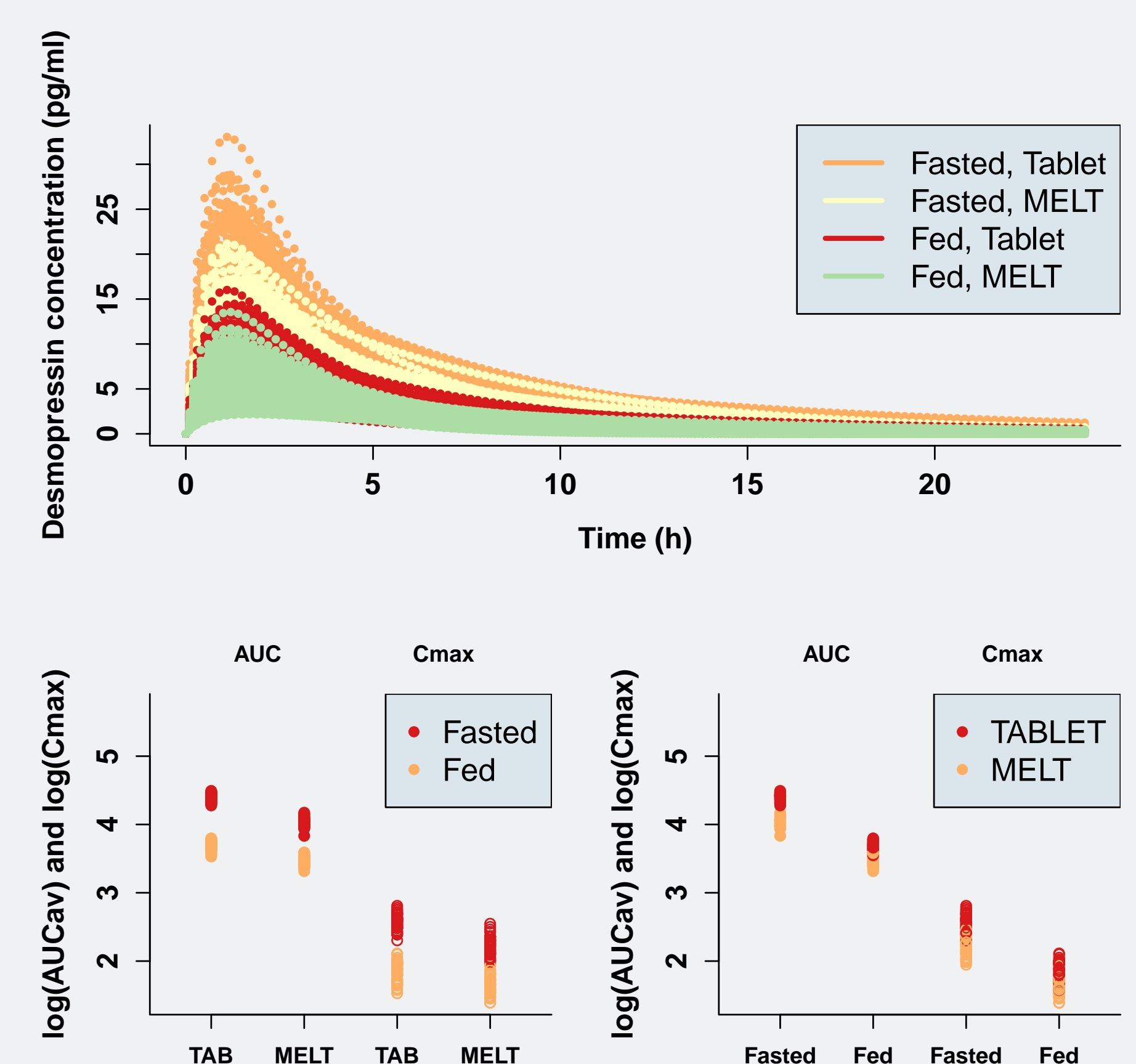


Figure 3: Top: Simulated DDAVP plasma concentrations (see text). Bottom: Comparison of the geometric mean AUC and C_{max} for the effect of formulation and food intake.

$AUC - ratio_{form} =$	138% [133% – 144%]
$C_{max} - ratio_{form} =$	144% [135% – 153%]
$AUC - ratio_{food} =$	194% [187% – 201%]
$C_{max} - ratio_{food} =$	202% [190% – 215%]

Acknowledgments

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