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Population pharmacokinetic model of mitotane enzyme autoinduction in adrenocortical carcinoma patients.

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Background & Objectives

- Mitotane is a first choice drug for the treatment of adrenocortical carcinoma (ACC).
- It has a remarkable inter-patient variability, a narrow therapeutic range and is subject to CYP3A4 auto-induction.
- Although therapeutic drug monitoring (TDM) is commonly used, it remains unclear which loading dose and TDM schedule would be optimal.

➢ The <u>objective</u> of this study is to develop a population pharmacokinetic model of mitotane and to investigate model-based optimizations of dosing regimens and TDM schedules.

Methods

- Plasma concentrations from TDM of 45 ACC patients receiving 0.5-10g mitotane per day (Table. 1) were analyzed using NONMEM®.
- A hypothetical enzyme compartment with enzyme synthesis depending on mitotane plasma concentrations was introduced to model autoinduction (Fig. 1), and a covariate model was developed to identify sources of variability.
- Simulations were performed to assess the probability of target attainment with different combinations of loading and maintenance doses (1-6g).

Characteristics	Total (n = 45)
Age, years [mean ± sd]	47 ± 14
Sex, female [n (%)]	29 (64.4)
BMI [mean ± sd]	24.8 ± 4.0
No. of dose administrations [median (IQR)]	16 (10.5 ; 22.5)
No. of measurements [median (IQR)]	13 (7.5 ; 20)

Table 1. Patient characteristics

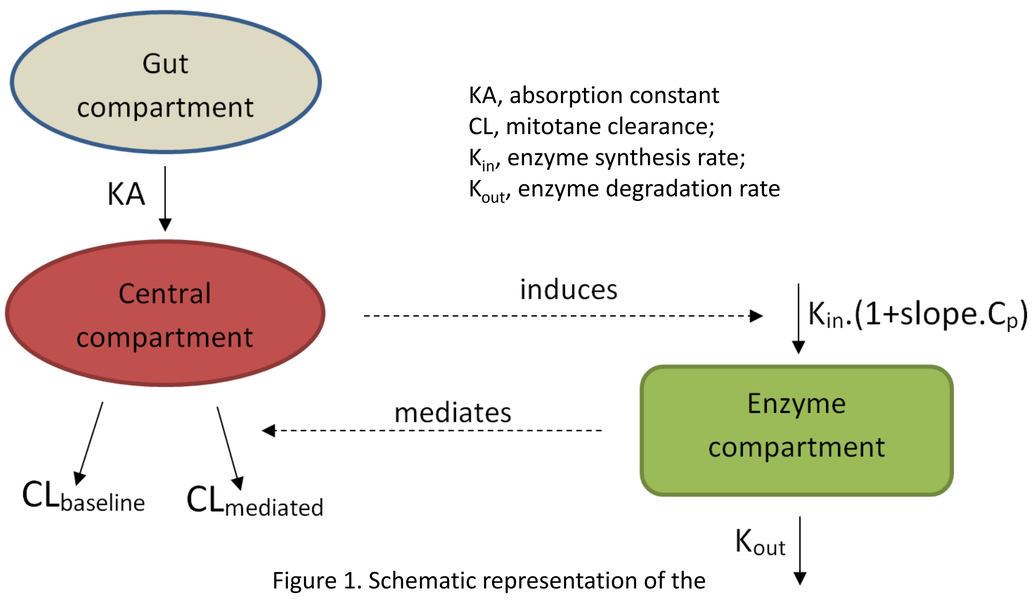

Figure 1. Schematic representation of the basic pharmacokinetic model

Results

- The suitable base model to describe the data was a one-compartment model with first order absorption (Fig. 2 & 3). High interindividual variability (IIV) was associated with both volume of distribution (V) and the baseline clearance (Table 2).
- An indirect response model with the change in enzyme linearly related to mitotane plasma concentrations described autoinduction appropriately. A 72-fold increase in enzyme synthesis rate was estimated for the median mitotane plasma concentration of 14.6mg/L.
- Individual body mass index and gender were identified as statistically significant covariates and reduced the IIV for V by 34%. Similarly, 25% of IIV for $CL_{baseline}$ was explained by individual triglyceride, γ-glutamyltransferase and creatinine plasma concentrations (Table. 2).

Parameter	Population mean estimate	CV (%)	
		(no covariates)	(covariate model)
Absorption constant	2.08* (1/hr)	-	-
Bioavailability	0.3*	-	-
Volume of distribution	3740 (L)	105%	71%
Baseline Clearance	0.0296 (L/hr)	89%	64%
slope	4.87	-	-
Enzyme degradation rate	0.019* (1/hr)	-	-

Table 2. Parameter estimates
*fixed according to literature
(Attivi *et al.*, Drug Developpment and Industrial Pharmacy. 2010; Jang et al., Current Drug Metabolism. 2008)

Results

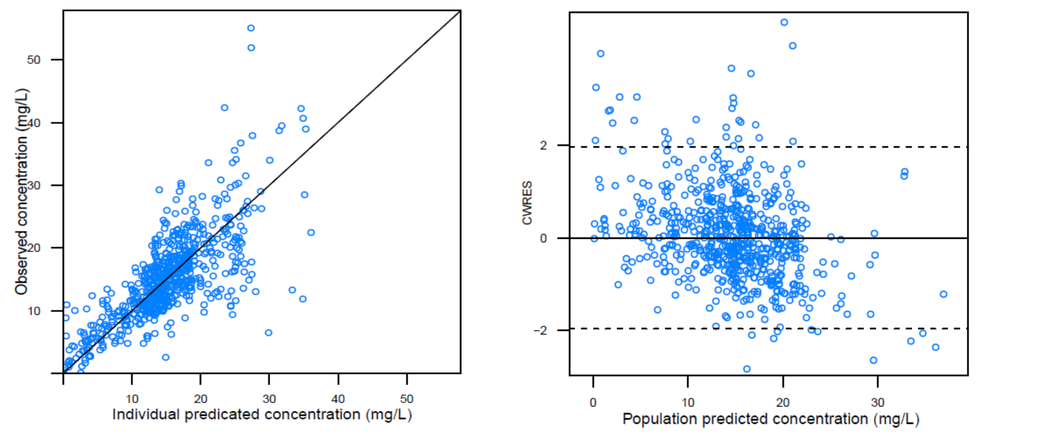

Figure 2. Goodness of fit plots

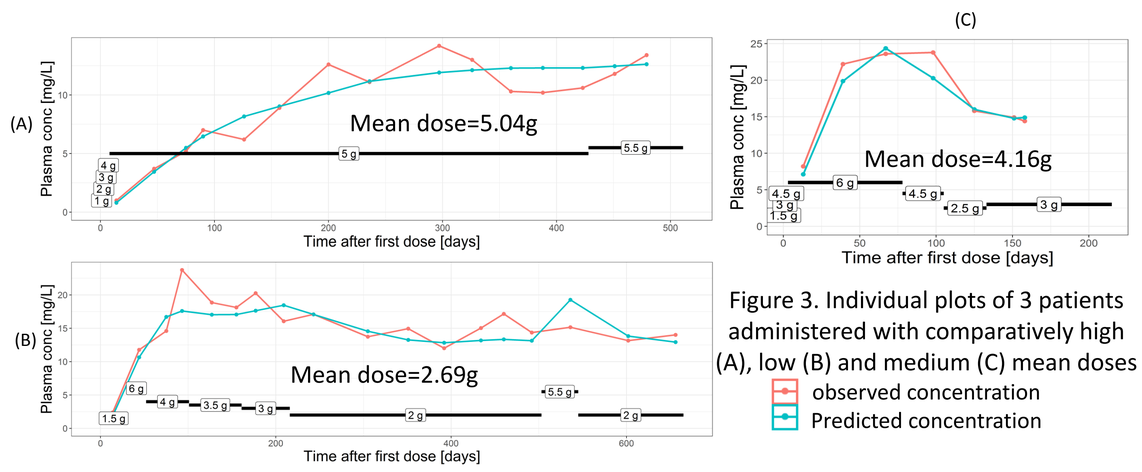

Figure 3. Individual plots of 3 patients administered with comparatively high (A), low (B) and medium (C) mean doses
observed concentration
Predicted concentration

- Simulations results suggest a high loading dose of 6g daily followed by a first TDM not later than day 11 to safeguard a high probability of target attainment and an appropriate adjustment of maintenance doses (Fig. 4).
- Time of target attainment can be predited from the results of first TDM using a linear model (Fig. 5).

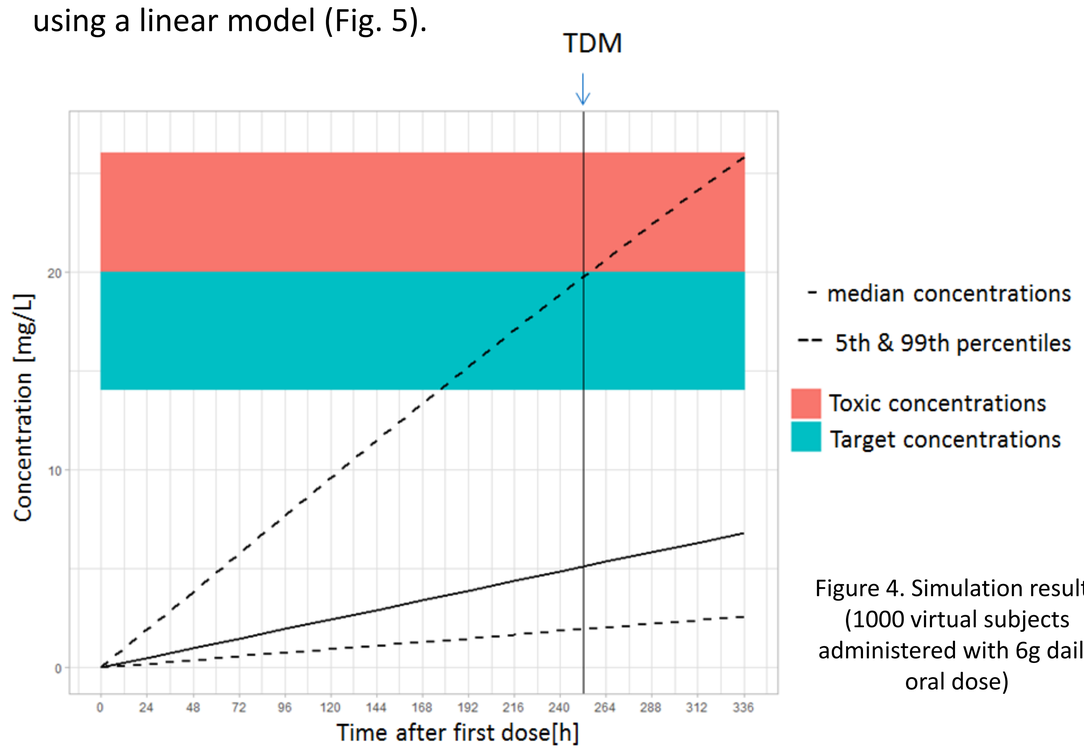

Figure 4. Simulation results (1000 virtual subjects administered with 6g daily oral dose)

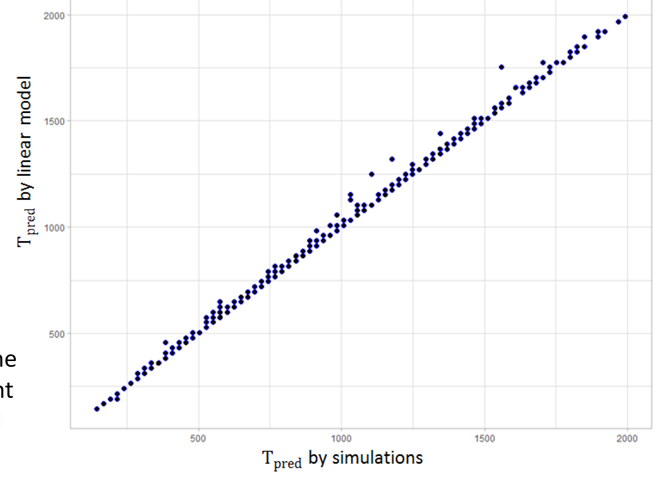

Figure 5
Precision in predicting the time of target attainment (T_{pred}) by linear model

Conclusions

- Our results support the clinical practice to use a high mitotane loading dose.
- The model facilitates the optimization of TDM and is a useful tool to establish individualized maintenance doses by forecasting individual plasma concentrations.

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