pharmaceutics

Supplementary Materials: Population Pharmacokinetics Modelling and Simulation of Mitotane in Patients with Adrenocortical Carcinoma: An Individualized Dose Regimen to Target All Patients at Three Months?

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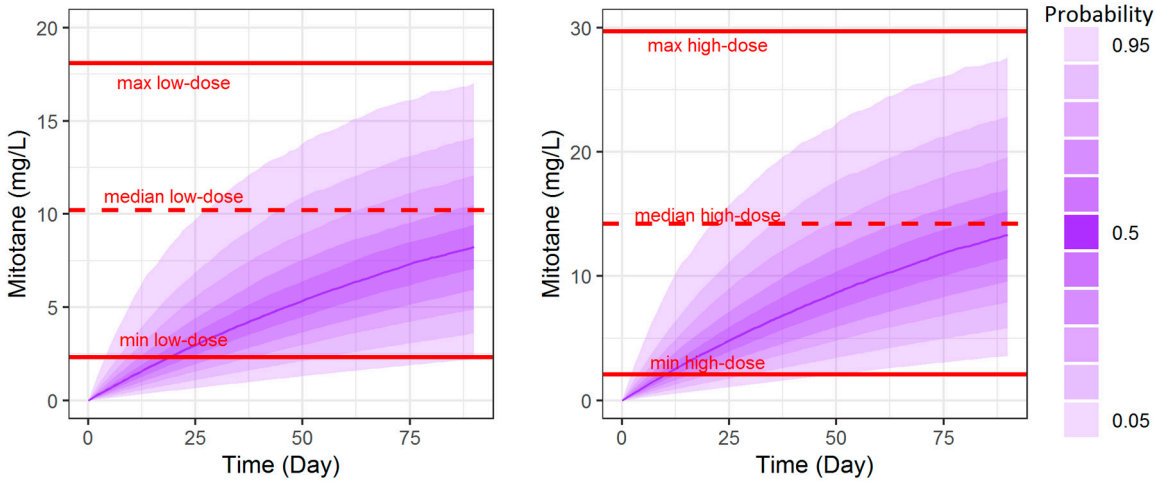

Figure S1. Comparison between simulated concentration profile from our final model versus median (min-max) value of mitotane at 84 days of therapy from study of Kerkhofs et al. [34].

Table S1. Summary of covariates model building and time-varying clearance.

Model	Number of Covariates	−2LL	BIC	ΔBIC	RSE of Parameters
Basic model (1 cmt)	0	3005	3027		< 30%
Tg on Cl (1cmt)	1	2994	3019	−8	< 30%
Tg and HDL on Cl (1cmt)	2	2988	3015	−12	< 30%
Tg, HDL and Lcat2 on Cl (1cmt)	3	2960	2093	−34	< 30%
Basic model with TVC Equation 6	0	2999	3030	−3	> 1000%
Arshad et al.[16]	1	3026	3051	+24	< 30%

Abbreviations are as follows: −2LL = -2 × loglikelihood; ΔBIC = BIC (model step) − BIC (basic model); RSE, Relative standard error; BIC, Bayesian information criterion; lcat2, latent covariate; Tg, triglyceride; TVC, Time-varying clearance.

Equation S1. Summary of equations to model a time-varying clearance.

$$Cl_{linear} = Cl_{initial} + k_{out} \times TIME \quad (1)$$

$$Cl_{exp} = Cl_{initial} \times e^{k_{out} \times TIME} \quad (2)$$

$$Cl_{initial\_exp} = Cl_{initial} + Cl_{ss} \times e^{k_{out} \times TIME} \quad (3)$$

$$Cl_{concave} = Cl_{initial} + Cl_{ss} \times (1 - e^{-k_{out} \times TIME}) \quad (4)$$

$$Cl_{Emax} = Cl_{initial} + Cl_{ss} \times \left(\frac{TIME^{\gamma}}{TIME^{\gamma} + T50^{\gamma}}\right) \quad (5)$$

$$Cl_{pheno1} = Cl_{ss} - (Cl_{ss} - Cl_{initial}) \times \left(\frac{T12}{T12 + TIME}\right) \quad (6)$$

$$Cl_{pheno2} = Cl_{ss} - (Cl_{ss} - Cl_{initial}) \times e^{\left(\frac{-TIME}{T12}\right)} \quad (7)$$

$$Cl_{mecha} = Cl \times \mathrm{ddt}_{\mathrm{Enz}}\left\{= K_{enz} - K_{enz} \times \left(1 - \frac{Cc}{Cc + IC_{50}}\right) \times Enz\right\} \quad (8)$$

Abbreviations are as follows: $Cl_{initial}$ clearance at time = 0, *Clss* induced clearance, k_{out} rate constant for the change in clearance rate. γ gamma (shape factor), *TIME* time after first administration, *T50* time at which clearance of the Cl_{Emax} model reaches 50% of its final value, *T12* time scale at which clearance change, *Cc* mitotane plasma concentration, K_{enz}.