Population pharmacokinetic and pharmacogenetic analysis of mitotane in patients with sadrenocortical carcinoma: towards individualized dosing

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Online Resource 2 Shiny app establishing method and results

Shiny app establishment

Based on the final mitotane population pharmacokinetic model, a Shiny app was established for the simulation for a random patient and to elucidate an example of the model application on guiding treatment for a new patient. Package shiny (version 1.4.0) and RxODE (version 0.6-1) in R statistics software (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria) were utilized. The R script can be found through: https://github.com/AnyueYin/Shiny-app-script-for-model-simulation---Population-PK-and-PG-analysis-of-mitotane. Patient gender, weight, and height, which were used to estimate lean body weight (LBW) and fat amount (FAT), as well as the results of three SNPs were in the input panel, based on which the starting dose was suggested. One hundred times of simulation under an optimized mitotane treatment regimen, Regimen 5-(-4g), were performed given the input information. The 90% prediction interval, 50th percentile of the predictions, target reaching time, and suggested starting dose were plotted in the output figure. The residual errors were not considered in the simulation.

Screen shots of the developed shiny app is shown in **Fig. S6**. The result shows that for a male patient with 85 kg weight and 180 cm height who carries G/G, A/A, and T/C for *CYP2C19*2* (rs4244285), *SLCO1B3* 699A>G (rs7311358), and *SLCO1B1* 571T>C (rs4149057), respectively, the 90% prediction interval can nicely locate within the therapeutic window of mitotane. The starting dose was suggested as 5.5g per day and the 50th percentile of the predictions reached the target on day 92. If the genotype result of *CYP2C19*2* (rs4244285) changed to G/A, the suggested starting dose became 4 g per day and the 50th percentile of the predictions reached the target on day 94.

In addition, a model with FAT effect on central distribution volume as the only covariate (**Table S3**) was also built in the Shiny app as an alternative option to allow dosing advice and concentration prediction for patients when genotyping results are not available (**Figure S6c**).

Table S3 Parameter estimates of the final model without genotyping results as covariates

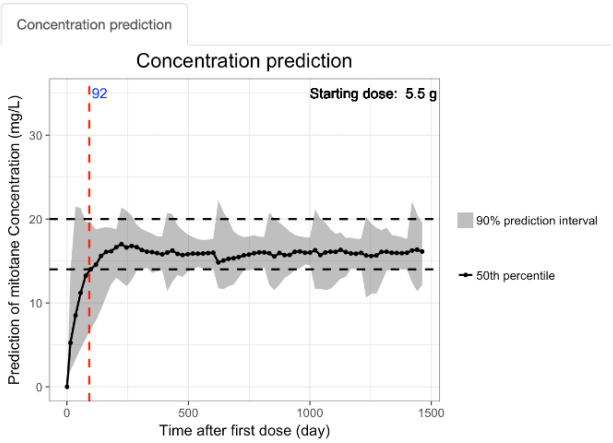
	Final model		
Parameters	**Estimate (RSE%)**	**IIV (CV%) [shrinkage]**	**IOV[a] (CV%)**
KA (/day)	15.0 fixed	-	-
CL/F (L/day)	217 (9%)	66.3 [7%]	31.2
V_c/F (L)	8450 (16%)	63.5 [37%]	-
V_c_FAT (power)	1.12 (18%)	-	-
V_p/F (L)	15500 (15%)	80.4 [36%]	-
Q/F (/day)	609 (28%)	100.5 [38%]	-
Residual errors			
PRO (CV%)	16.7 (6%)	-	-
ADD (mg/L)	0.907 (16%)	-	-

FAT, fat amount; RSE, relative standard error; CV, coefficient of variation; IIV, inter-individual variability; IOV, inter-occasion variability; PRO, proportional residual error; ADD, additive residual error; CL/F, apparent system clearance; KA, absorption rate constant; V_c/F, apparent distribution volume of central compartment; V_p/F, apparent distribution volume of peripheral compartment; Q/F, apparent distribution rate constant;

[a] Every 200 days of dosing was defined as an occasion

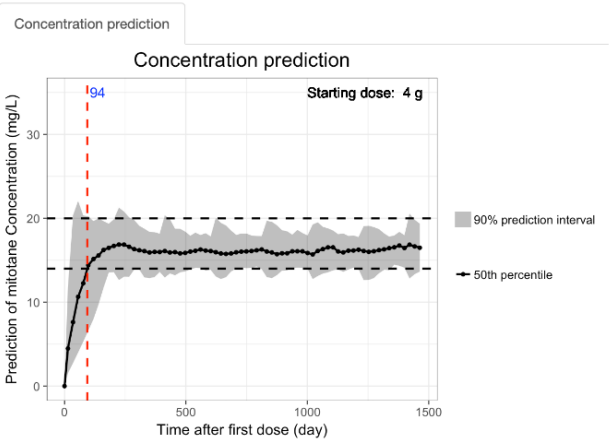
a **Mitotane**

Characteristics of patients:
Is genotyping results available? YES
CYP2C19*2 (rs4244285) G/G
SLCO1B3 669A>G (rs7311358) A/A
SLCO1B1 571T>C (rs4149057) T/C
Weight of patient (kg) 85
Height of patient (cm) 180
Gender of patient (F/M) F / M
Plot



b **Mitotane**

Characteristics of patients:
Is genotyping results available? YES
CYP2C19*2 (rs4244285) G/A
SLCO1B3 669A>G (rs7311358) A/A
SLCO1B1 571T>C (rs4149057) T/C
Weight of patient (kg) 85
Height of patient (cm) 180
Gender of patient (F/M) F / M
Plot



c **Mitotane**

Characteristics of patients:
Is genotyping results available? NO
Weight of patient (kg) 85
Height of patient (cm) 180
Gender of patient (F/M) F / M
Plot

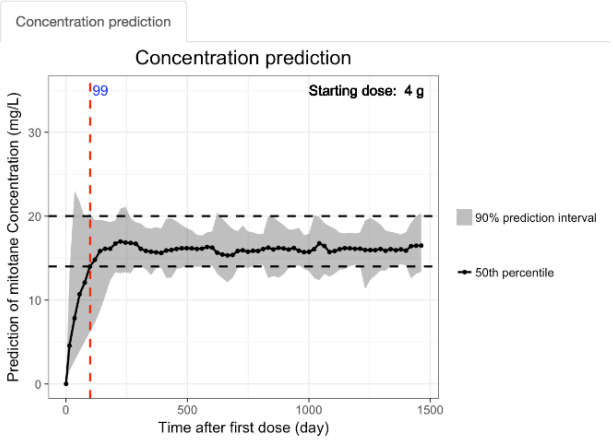


Fig. S6. Screen shot of the shiny app established based on the final model. a) a male patient with 85 kg weight and 180 cm height who carries G/G, A/A, and T/C for *CYP2C19*2* (rs4244285), *SLCO1B3* 699A>G (rs7311358), and *SLCO1B1* 571T>C (rs4149057), respectively. b) a male patient with 85 kg weight and 180 cm height who carries G/A, A/A, and T/C for *CYP2C19*2* (rs4244285), *SLCO1B3* 699A>G (rs7311358), and *SLCO1B1* 571T>C (rs4149057), respectively. c) a male patient with 85 kg weight and 180 cm height whose genotyping results are unknown.