Tobramycin dose individualization using the MonolixSuite

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Introduction

Dose individualization has been shown to improve patient outcomes.

How can dose individualization be done in practice?

Tobramycin (aminoglycosides) has a narrow therapeutic window and could benefit from dose individualization.

An example with Tobramycin

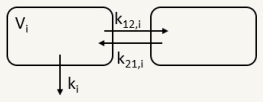
Model development

Stepwise model development, based on clinical data published in Aarons et al.

- sparse data for 97 individuals
- repeated bolus administrations

Final model:

1. Structural model:



2. Parameter distribution / covariates:

$$k_i = k_{pop}\left(\frac{CLCR}{67.8}\right)^{\beta_{k,CLCR}}\left(\frac{WT}{66.4}\right)^{\beta_{k,WT}} e^{\omega_k \eta_{k,i}}$$

$$V_i = V_{pop}\left(\frac{WT}{66.4}\right)^{\beta_{V,WT}} e^{\omega_V \eta_{V,i}}$$

$$k_i^{12} = k_{pop}^{12} \qquad k_i^{21} = k_{pop}^{21}$$

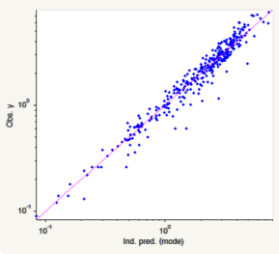
covariates
pop. parameters
random effects

3. Parameter estimates:

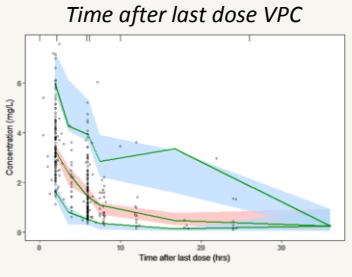
Parameter	Estimates (RSE)	IIV as %CV (RSE)
k_{pop} (/hr)	0.21 (7%)	29% (9%)
$\beta_{k,CLCR}$	0.89 (7%)	-
$\beta_{k,WT}$	-1.09 (25%)	-
V_{pop} (L)	19.8 (6%)	11% (55%)
$\beta_{V,WT}$	0.80 (36%)	-
$k12_{pop}$ (/hr)	0.041 (111%)	-
$k21_{pop}$ (/hr)	0.12 (84%)	-

4. Diagnostic plots:

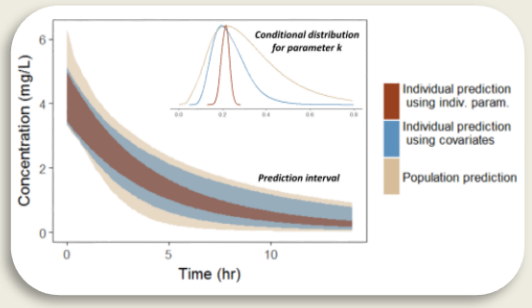
Obs. versus Pred.



Time after last dose VPC



Key idea



Use prediction interval derived from:

- covariates
- therapeutic drug monitoring

... to adapt the dose.

Workflow

Datxplore (visualization)

Obtain clinical data on Tobramycin pharmacokinetics

Develop a popPK model, with IIV partly explained by covariates

Monolix (param. estim.)

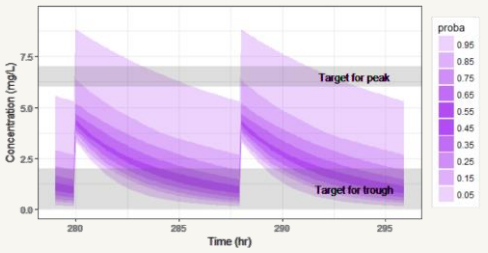
Use the model for optimal dose finding via simulations

Simulx (simulations)

Dose individualization

1 Efficacy of default treatment (1mg/kg)

- Re-sample individuals from data set
- Draw individual parameters
- Simulate concentration for repeated doses

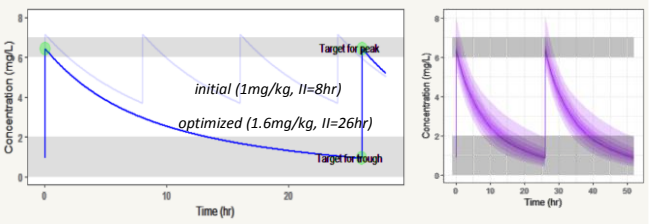


Chances to be efficient: 17%
Chances to be non-toxic: 77%

→ individualization

2 Dose optimization from covariates

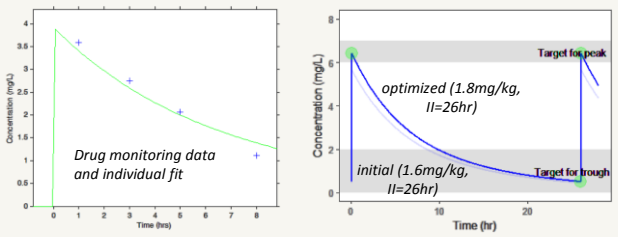
- Specific individual with WT=78 and CLCR=30
- Dose optimization via simulations

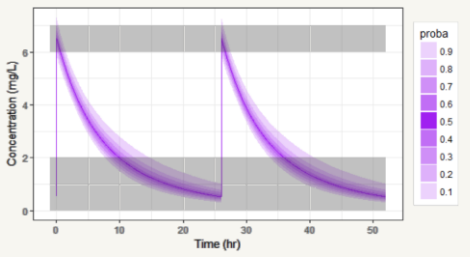


Chances to be efficient: 74%
Chances to be non-toxic: 93%

3 Dose optimization from indiv. parameters

- Individual data via therapeutic drug monitoring
- Individual parameter estimation via MCMC, given data + population parameters
- Dose optimization via simulations





Chances to be efficient: 84%
Chances to be non-toxic: 99%