Tobramycin dose individualization using the MonolixSuite

Authors: Geraldine Ayral (1), Marc Lavielle (2)(3), Jonathan Chauvin (1)

Affiliations: (1) Lixoft, Antony, France, (2) Center of Applied Mathematics, Ecole Polytechnique, Palaiseau, France, (3) Inria Saclay – Île-de-France, Palaiseau, France

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Objectives: The concept of personalized medicine has long been promoted to bring more benefits to patients, in particular by adapting the administrated dose to the patient’s characteristics. Methodologically and practically, dose individualization is a challenging task. We show how this can be done in an efficient way using the MonolixSuite.

Methods: We use the antimicrobial agent Tobramycin, which has a narrow therapeutic index. Using the non-linear mixed-effect model and data published in [1], we performed simulations to determine (i) if the typical treatment is safe and efficient, and (ii) the dose that would be most likely to be safe and efficient.

Results: The default dosing regimen of 1mg/kg every 8 hours is safe in only 75% of the simulated healthy individuals, calling for an individualization of the dosing regimen. We thus used the individual covariates to predict via simulations the concentration distribution for one specific individual taking into account the residual random effects. We implemented a simple optimization algorithm to determine a priori the dose that has the highest chance of being safe and efficient. If in addition, early drug monitoring permits to measure the drug’s concentration at a few time points after the initial dose, these data can be used to obtain the distribution of the individual’s parameters, using the Markov Chain Monte-Carlo procedure implemented in the Monolix software. We show that 4 measurements permit to significantly reduce the concentration prediction interval for this individual.

Conclusion: This example shows how a personalized treatment can be realized using population PK modeling and simulation, and how the MonolixSuite facilitates an efficient implementation.