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Statistical interaction modeling in non-linear mixed effect models: a case study in neonatal pharmacology

Laura B. Zwep (1), Anne van Rongen (1), Karel Allegaert (2,3,4), Catherijne A.J. Knibbe (1, 5, 6), Rob C. van Wijk (1)

(1) Division of Systems Pharmacology and Pharmacy, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands; (2) Department of Development and Regeneration, KU Leuven, Leuven, Belgium; (3) Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; (4) Department of Hospital Pharmacy, Erasmus MC, Rotterdam, The Netherlands; (5) Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; (6) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands

Laura Zwep

Poster: Methodology - New Modelling Approaches

Introduction

Covariate analysis is a crucial step in nonlinear mixed-effects (NLME) modeling to enable individualized dose and treatment optimization. Covariates can explain part of the inter-individual variability of a parameter in the model. In linear statistical modelling, next to these direct covariate effects, the influence of a covariate on a parameter can be moderated by a second covariate, generally called an interaction effect. This interaction allows the estimate for a covariate to change over the range of another covariate, by adding the product of the covariates as interaction term [1,2]. Interaction should not be confused with correlation, since it only captures variability in the case of (partially) uncorrelated covariates.

In neonatal pharmacology, some covariates that are important for clearance have large variability, e.g. gestational age (GA), birth bodyweight (bBW) and postnatal age (PNA). For most neonates, the bBW corresponds to their GA. However, for small for gestational (SGA) neonates, as defined by a bBW less than the 10^{th} percentile of the bBW for their GA, the bBW does not correspond to their GA. Therefore, SGA is an example of how the influence of bBW on clearance is moderated by GA. However, SGA is a dichotomous covariate, and this dichotomization can reduce statistical power and can change the parameter estimation depending on the chosen cut-off point [3]. A statistical interaction term can be used instead to include this moderation effect as a continuous covariate. However, such interaction term has not been previously defined in a NLME modeling framework.

Objectives

We aim to (1) translate the statistical interaction term of the linear statistical modeling to the NLME modeling framework, and (2) test the performance of the interaction as continuous covariate in the context of vancomycin clearance in comparison to SGA as dichotomous covariate in a case example.

Methods

Interaction term
In order to define an interaction term for non-linear functions, we used a clearance parameterization with two covariates with a standard power function for each covariate. We log-transformed this non-linear power function to a linear scale. Next, we added an interaction on this linear scale as $\theta_{i:j} \cdot log(x_i) \cdot log(x_j)$., where x_i and x_j represent two interacting covariates and $\theta_{i:j}$ the effect parameter. Finally, we transformed the equation back to a power scale, by exponentiation.

Case example: Vancomycin
To test the interaction term, we used a vancomycin dataset consisting of 437 (pre)term neonates with a median (range) GA of 30 (23-41) weeks and bBW of 1310 (385-4680) grams [4,5]. We used a simplified base model with the covariates GA and bBW, modeled as a power function for typical clearance ($CL_{tv}=\theta_1 \cdot BW^{\theta_2} \cdot GA^{\theta_3}$). We compared the base model to two extended models: one where SGA was added as dichotomous covariate on clearance, and another where the statistical interaction term was added as continuous covariate on clearance. Modelling was done in NONMEM 7.5, and we tested statistical improvement through the objective function value (OFVs) with the likelihood ratio test.

Results

After exponentiation of the log-transformed power function, the interaction term is defined as $(x_i^{log(x_j)})^{\theta_{i:j}}$. This term was used in the interaction model for vancomycin clearance.

The OFV for the base model with bBW and GA on clearance was 4352.2. For the SGA model with bBW, GA, and SGA on clearance, we found no significant improvement (dOFV=-1.14). The interaction model with bBW, GA, and the interaction on clearance, did show a small but significant improvement over the base model (dOFV=-4.91), indicating that the effect of bBW on clearance is modified by the value of GA. More specifically, it was found that with increasing GA the effect of bBW on clearance was smaller, indicating that bBW has less influence on vancomycin clearance for higher GA. The sensitivity analysis with a subset of the data concerning PNA showed similar results.

Conclusion

We defined an interaction term for covariate power functions in NLME models, which showed a statistically improved model in a covariate analysis for vancomycin clearance in a neonatal population compared to the alternative dichotomized covariate. This interaction term can be used in covariate functions other than the power function. We believe the use of the statistical interaction term can facilitate capturing interaction effects between two or more covariates, without the need for dichotomization.