Pharmacokinetic design optimization in children and estimation of maturation parameters: example of cytochrome P450 3A4

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Introduction

•Drug PK in children is different from those in adults, because of growth and maturation:

-Growth taken into account via ***allometric equation***

-Equation describing CYP3A4 maturation (MAT) was published: *(Johnson et al. 2006)*

$$MAT = \frac{PNA^{\theta}}{PNA^{\theta} + PNA_{50}}$$

MAT is the fraction of adult cytochrome P450 (CYP) abundance, PNA is the post-natal age in years, θ is the Hill coefficient, and PNA50 is the PNA at which CYP abundance is 50% that of the mature value. PNA50 and θ values are cytochrome-dependant variables.

• **Aim of this work**: to determine whether ***optimizing the study design in terms of ages and sampling times*** for a drug eliminated solely via cytochrome P450 3A4 (CYP3A4) would allow to accurately estimate the pharmacokinetic parameters throughout the entire childhood timespan, while taking into account age- and weight-related changes.

Material and methods

1. **Identification of optimum ages** with regards to maturation parameters of the maturation function using ***Pfim 3.0*** to create optimized demographic databases. *In this part of our work, the pharmacokinetic model normally used was replaced by the CYP3A4 maturation equation defined above.*

2. **Identification of post-dose sampling times**, for each age previously identified using ***Pfim 3.0***, to create optimized sparse sampling databases.

3. **Simulation of concentrations** using the "optimized sparse sampling databases" and the theoretical ("true") PK and maturation parameters using NONMEM. These databases, containing the simulated concentrations, were called "optimized concentration databases." Structural model: monocompartmental model with first-order absorption and linear elimination with Cl/F of 24 L/hour, Vd/F of 66.5 L, ka of 1.5 h-1).

$$Cl/F = TV_{(Cl/F)} \cdot \frac{PNA^{0.83}}{PNA^{0.83} + 0.31} \cdot \left(\frac{BW}{70}\right)^{0.75}$$

$$Vd/F = TV_{(Vd/V)} \cdot \left(\frac{BW}{70}\right)$$

4. **Pharmacokinetic parameter estimation** performed on the optimized concentration databases using NonMem.

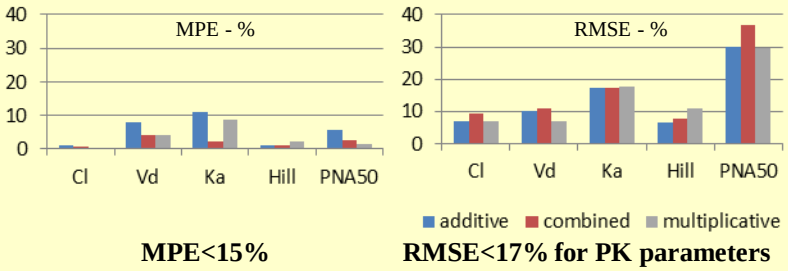
5. **Comparisons of true and estimated parameter values**

Results

• **Established optimised design:**

with three or four samples per subject, in accordance with the residual error model.

•**Estimated population parameters estimated with this design:**



MPE<15%

RMSE<17% for PK parameters

Discussion

• PK parameters estimations are unbiased and precise

•maturation parameters estimations are unbiased but less precise

•taking growth and maturation into account *a priori* in a pediatric pharmacokinetic study is **theoretically feasible**.

•requires that **very early ages be included in studies**, which may present an obstacle to the use of this approach.

•First-pass effects, alternative elimination routes, and combined elimination pathways should also be investigated.