

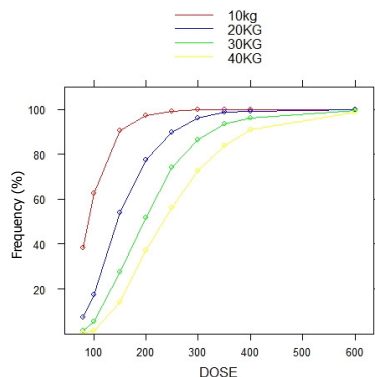
Title: Dose bridging in paediatric indications.

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Objectives: Dose recommendation for paediatric indications remains a major challenge in early clinical development. The rationale for dose selection and dosing regimen in clinical trials is often determined by a trial-and-error approach. Most importantly, medical practice assumes linear, direct relationships between body size, physiological function and response. In the current investigation, we explore different pharmacostatistical methodologies to identify a descriptor of developmental changes that can be used as covariate for dose adjustment in children. The proposed approach is illustrated for the antiviral drug abacavir.

Methods: Data from six pharmacokinetic studies in adults (n=111) and one study in paediatrics (n=14) were analysed using nonlinear mixed effects modelling, as implemented in NONMEM VI. The analysis was aimed at assessing whether parameter distributions differed between populations and whether such differences affected systemic exposure to abacavir. In addition to the standard stepwise covariate analysis based on demographic factors, data were evaluated according to a random (mixture model) and an arbitrary (clustering) dichotomisation of the study populations. The contribution of adult data for estimation of pharmacokinetic parameter distribution in children was assessed by concomitant data analysis and by a Bayesian approach in which adult data is used as priors. Simulations were used to estimate dosing regimen in children.



Results: Estimates from mixture models show that clearance distribution does not reflect group demographics. Rather, a considerable overlap is observed in parameter values in the two populations. Body weight was found to be a covariate for clearance and volume, explaining a considerable part of the differences in the pharmacokinetics of abacavir in the paediatric population. The use of priors for model parameters improved the accuracy of estimates and reduced model bias compared to the concomitant data analysis with unbalanced number of children and adults. To ensure abacavir exposure equivalent to adults, dose adjustment in children should be based on a non-linear function of body weight.

Conclusion: Our analysis shows the value of integrated pharmacokinetic modelling of adult and paediatric data in early clinical development. The pharmacokinetics of abacavir in children differs from adults in terms of clearance and volume. Dose adjustment based on body weight can be used as a covariate for dose adjustment in the young. Furthermore, simulations reveal that systemic exposure can be accurately estimated in a small population. This methodology can therefore be used in the interim analysis of paediatric clinical trials, offering a better alternative to dose selection in early paediatric development.

References:

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