Paediatric pharmacokinetic studies could be optimized for the precision of the clinically relevant exposure endpoint instead of PK parameter precision

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Introduction

Exposure-matching with reference or adult population is one way to establish a drug's benefit-risk balance in children [1] and requires accurate characterization of PK in children. It has been proposed that paediatric PK studies should be powered to have confidence intervals for clearance (CL) and volume of distribution (Vd) within a pre-specified range [2]. However, Vd may be more influential for drugs whose effects are driven by peak concentrations or early exposure measures, whereas CL is more directly related to steady-state exposure metrics such as AUC. Methods are needed to explicitly link parameter precision to precision in clinically relevant exposure metrics to align paediatric study design with decision-making objectives.

Methods

A linear two-compartment PK model with low clearance, theory-based allometry and a fixed maturation function was used. Expected precision of exposure metrics was calculated for age-groups of <2 years, 2 to <6 years, 6 to <12 years, 12 to <18 years, and adults. Representative weights were simulated as a function of age assuming full-term gestation[3].

To prevent information sharing between adults and children, the model was parameterized to estimate CL, Vc and Vp uniquely for each age-group; a "risk-based" assessment was conducted for these parameters.

Two different clinical use scenarios were considered:

- Scenario 1, in which Cmax after a single dose was the clinically relevant driver of the drug effect
- Scenario 2, in which the steady-state Cavg upon QD dosing was the clinically relevant drug effect driver.

The study design of each scenario is illustrated in **Figure 1**.

Doses were set to be on mg/kg basis, with a 70 kg adult receiving a 100 mg dose. The expected Fisher Information was calculated based on previously published equations [4,5]. Monte Carlo simulations were used to propagate variance-covariance in PK parameters to precision in single-dose Cmax and steady-state Cavg.

Results and discussion

In Scenario 1, Cavg precision was low in paediatric age-groups, and the Cmax precision was higher. Conversely, in Scenario 2 Cmax precision was low and Cavg precision high **(Table 1; Figure 1)**. Steady-state Cavg precision was virtually identical to clearance precision, as expected from established PK theory on AUC and clearance being proportional **(Table 1)**.

These findings illustrate that a study design can result in the clinically relevant exposure measure being captured with high precision, even if not all paediatric PK parameters are captured with high precision. The theoretical example here was chosen demonstrate a clear difference between two distinct endpoints, the steady-state Cavg versus single-dose Cmax. It is recognized that in real-world scenarios, several endpoints relating to e.g. efficacy and safety may need to be considered simultaneously. The demonstration of this framework using real-world case examples is a topic for future research.

Conclusion

Paediatric study designs should consider focusing on the expected precision of the clinically relevant exposure measure, instead of on the expected precision of CL and Vd.

Table 1. Expected relative standard errors in the PK endpoints Cavg and Cmax by MC sampling of parameters from variance-covariance matrix, and the age-group specific relative standard errors in CL, Vc, Vp and Q. The values refer to the relative standard error of prediction for a typical subject in each age group. For the four paediatric age groups, a range of relative standard errors is reported for reasons of conciseness.

Variable	Scenario 1	Scenario 2
Cavg	59.1% for adults, 40.7-73.7% for children	8.75% for adults, 9.97-11% for children
Cmax	15.3% for adults, 17.3-19.3% for children	69.1% for adults, 76-103% for children
CL	58.5% for adults, 39.9-73.3% for children	8.73% for adults, 9.88-11% for children
Vc	58.6% for adults, 62.2-75.1% for children	168% for adults, 183-255% for children
Vp	37.3% for adults, 31.4-46.8% for children	67.3% for adults, 69.9-81.9% for children
Q	9.69% for adults and children	28.8% for adults and children

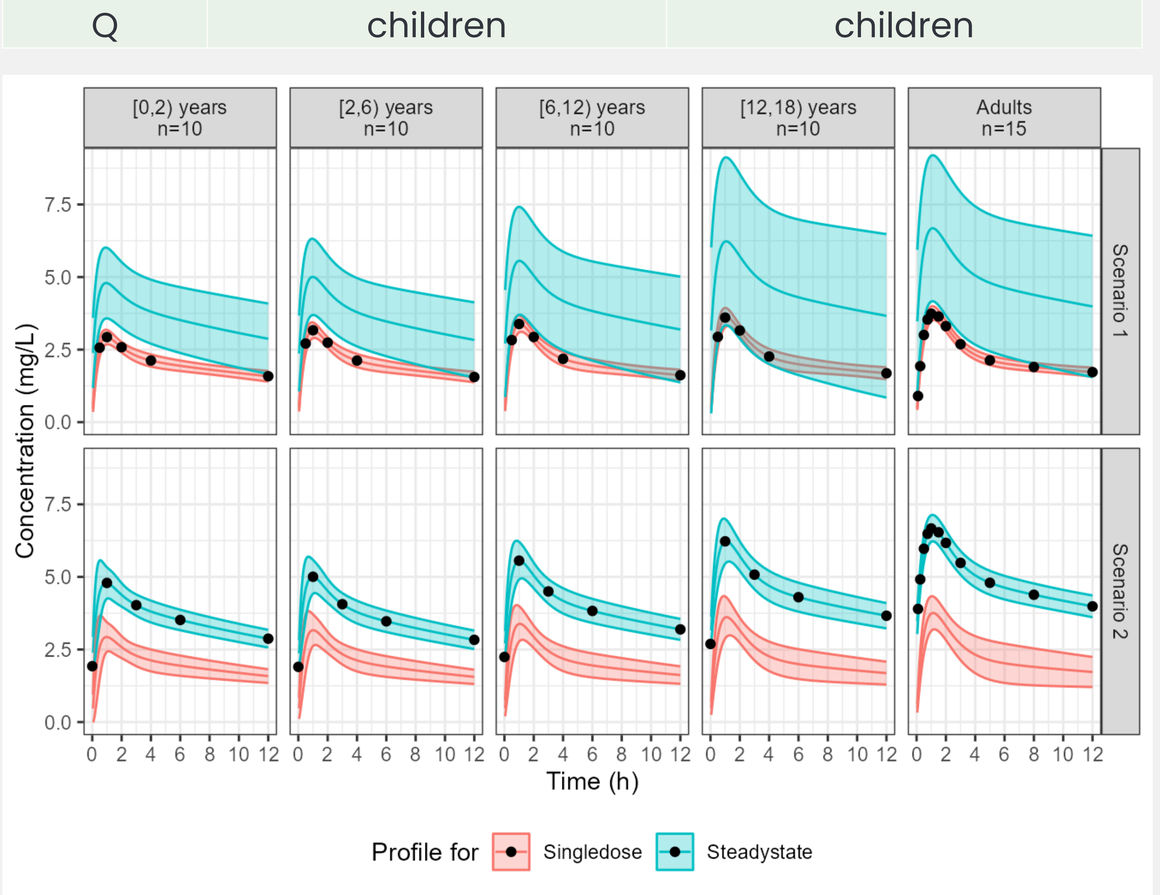

Figure 1. Predicted uncertainty in the single-dose and steady-state concentration profiles for representative individuals, given the study design. Rows denote scenario, columns denote age groups. Shaded region denotes 68% CI (± 1 standard error if the observations were normally distributed). The confidence interval has been calculated via Delta Method. Points denote PK sampling times.

References

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