What Sample Size to Use When Designing Paediatric Pharmacokinetic Studies? A Critical Analysis of "Precision Criteria"

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Background

A new approach for calculation of sample size in paediatric clinical pharmacokinetic (PK) studies has been suggested based on desired precision for PK parameter of interest[1]. In this approach a clinical study is designed to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of the PK parameter with at least 80% power. The method requires an estimate of variability for the parameter. The estimate of variability could be obtained from different sources such as 1) the standard deviation (SD) from prior PK studies undertaken in adults, 2) SD reported in conventional paediatric PK studies with a limited sample size or 3) predicted SD for PK parameters from physiologically based pharmacokinetic (PBPK) models combined with *in vitro-in vivo* extrapolation (IVIVE). A recent study indicated that although the SD of individual PK values for adults are typically used to provide the estimate, this approach leads to inaccurate predictions by not taking into account the more widespread distribution of factors such as body weight in the paediatric population[2]. It is not known whether the three sources mentioned above lead to significantly different estimates of sample size.

Methods

Selection of compounds and data collection

Compounds were selected based on availability of PK data in both adults and children of various age groups. Since PBPK simulations for estimating SD were carried out using the Simcyp[3] simulator, availability of compounds in the Simcyp library was also considered. The selected compounds included caffeine, ibuprofen, midazolam, itraconazole and theophylline. A comprehensive literature review was undertaken to collect data on two PK parameters: clearance (CL) and volume of distribution (V_d).

Data analysis to get the variability using;

Observed data as the source of variability: An estimate of variability for the PK parameter of interest was obtained by conducting meta-analysis on CL (L/h/kg) and V_d (L/kg) in both adults and paediatric groups. The latter group was stratified into neonates (birth to1 month), infants (1 month to 2 years) and children (2 years to 12 years). Pooled variance Δ^2 and weighted mean $\bar{\mu}$ were obtained from equations 1 and 2.

$$\Delta^2 = \frac{\sum_{i=1}^{N_s}(n_i - 1)S_i^2}{\sum_{i=1}^{N_s}(n_i - 1)} \qquad \text{Equation 1}$$

where n_i and S_i are the number of subjects and the SD of the i^{th} study and N_s is the number of studies.

$$\bar{\mu} = \frac{\sum_{i=1}^{N_s} n_i \times \mu_i}{N} \qquad \text{Equation 2}$$

Where μ_i is the mean of the parameter in i^{th} study and N is the sum of the number of subjects in all studies.

Coefficient of variation (CV) was calculated from $\bar{\mu}$ and squared root of Δ^2. Log-transformed SD (δ) was calculated using equation 3.

$$\delta = \sqrt{\ln(1 + CV^2)} \qquad \text{Equation 3}$$

PBPK simulations as the source of variability: 1000 simulations were carried out to predict the CL and V_d for the five compounds in neonates, infants and children and δ was calculated form the simulated mean and SD.

Sample size calculation

Wang *et al*.,[1] provide an R code for calculation of sample size. The calculated δ was entered into Wang's code[1] and sample size was calculated.

Results

As expected there were variations in estimates of sample size depending on the parameter and source of estimated variance used to derive the values. Estimated sample sizes using various methods (the SD from prior PK studies undertaken in adults, SD reported in conventional paediatric PK studies with a limited sample size or predicted SD for PK parameters from PBPK models) for five drugs (caffeine, ibuprofen, midazolam, itraconazole and theophylline) and different PK parameters (CL and V_d) are presented in the figure below.

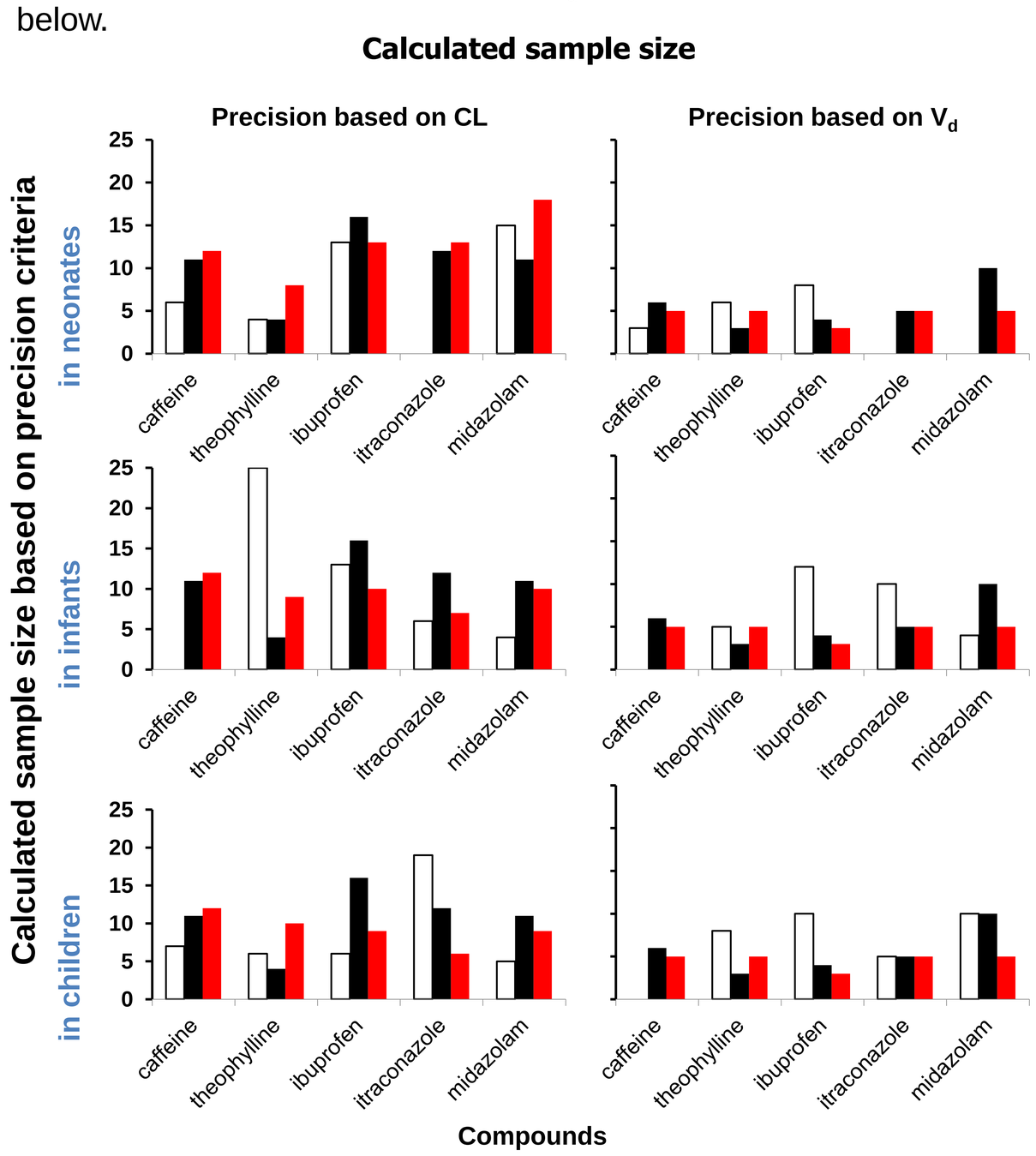

Figure. Left and right columns show sample size calculated from variability around CL and V_d, respectively. Top, middle and bottom panels show the calculated sample seize for neonates, infants and children.

Discussions & conclusions

There was no consistent discrepancy in the sample size calculated according to the source of variability entered into the sample size calculations and therefore an overall trend could not be established with regard to whether paediatric, adult clinical PK studies or PBPK simulations lead to higher or lower variability.

The calculated sample size from observed paediatric groups and adult SDs were significantly different in over 70% of cases whereas a recently published study did not report any significant difference between adult and paediatric CVs[2]. The latter study only compared the CVs in children 6 years and over with adults and did not investigate the variability in neonates and infants. Variability around simulated PK parameters from PBPK models could be used to calculate the sample size although in our study it led to significantly different sample sizes from paediatric observed SDs in 60% of the cases.

A conservative approach should be taken when using 'precision based methodology' knowing that various sources of initial estimates of variability will not lead to similar sample size calculations. Further studies are required to acquire more reliable estimates of variability.

References

1. Wang Y, *et al.* (2011) Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies. *J Clin Pharmacol*.
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