The allometric exponent for propofol clearance varies with age

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Introduction

For scaling clearance to pediatrics, the allometric scaling function is used in occasions either having both adult data and pediatric data together or having only pediatric data. In order to investigate the influence of the different combinations of datasets on the allometric scaling exponent of propofol clearance, we studied the allometric exponents of propofol clearance in different populations which are grouped both by the study population and by the age range of the FDA guidance.

Methods

Seven previously published propofol studies [1,2,3,4,5,6,7] were included in the analysis. The data were grouped by the study population into six datasets (***Table 1***) and grouped by the age range from the FDA guidance for pediatric study [8] into five datasets (***Table 2***).

For the analysis grouped by the study population, we systematically selected two out of six datasets in two ways:

- one pediatric dataset and one adult dataset
- two pediatric datasets

For the analysis grouped by the FDA guidance [8], we selected two out of five datasets which comprised one pediatric dataset and one adult dataset. We performed the population pharmacokinetic analysis using NONMEM 7 on each of the combined datasets with a three-compartment model together with an bodyweight allometric scaling model for the clearance, in order to estimate the exponents (EXP_{CL}) for different data composition.

Table 1. *Summary of the datasets grouped by the study population.*

Study population	Investigator	N	Age	Bodyweight
Neonate	Allegaert[1]	25	1 - 25 days	0.68-4.03 kg
Infant	Peeters[2]	20	3.8 -17.3 month	4.8 -12.5 kg
Toddler	Murat[3]	12	1 - 2.6 years	8.74 - 18.9 kg
Child	Kataria[4]	53	3 - 11 years	15 - 60.5 kg
Adolescent	Blussé van Oud-Alblas[5]	14	9.6 - 19.8 years	36.6 – 82 kg
Adult	Knibbe[6] & Schnider[7]	48	27 - 81 years	44.4 – 80 kg

Table 2. *Summary of the datasets grouped by the FDA guidance for pediatric study*

Pediatric Subpopulation	N	Age	Bodyweight
Newborn	25	0-1 month	0.68-4.03 kg
Infant	31	1 month – 2 years	4.8-14.2 kg
Child	58	2 – 12 years	11.2-74 kg
Adolescent	12	12 – 16 years	40-82 kg
Adult	48	Above 16 years	44.4-122 kg

[1] Allegaert, K., et al. Br J Anaesth, 2007
[2] Peeters, M.Y., et al., Anesthesiology, 2006
[3] Murat, I., et al., Anesthesiology, 1996
[4] Kataria, B.K., et al., Anesthesiology, 1994
[5] Blussé van Oud-Alblas, H.J., et al., in submission
[6] Knibbe, C.A., et al., Br J Clin Pharmacol, 1999
[7] Schnider, T.W., et al., Anesthesiology, 1998
[8] FDA Guidance for industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products, 1998

Results

In the analysis grouped by the study population, the estimated allometric scaling exponent varied from 0.57 to 1.15 when the data was composed of one pediatric dataset and one adult dataset (***Table 3***). It varied from 0.2 to 2.01 when the data was composed of one pediatric dataset and another pediatric dataset (***Table 4***)

In the analysis grouped by the FDA guidance, the estimated allometric scaling exponent varied from 0.61 to 1.15 (***Table 5***), which was very similar to the results in the analysis grouped by the study population.

No	Dataset 1	Dataset 2	EXP_{CL}
I	Neonate	Adult	1.15
II	Infant	Adult	0.57
II	Toddler	Adult	0.74
IV	Child	Adult	0.64
V	Adolescent	Adult	0.81

Table 3. *Estimated EXP_{CL} for the combinations of one pediatric dataset and one adult dataset in the analysis grouped by the study population.*

Table 4. *Estimated EXP_{CL} for the combinations of two pediatric datasets in the analysis grouped by the study population.*

No	Dataset 1	Dataset 2	EXP_{CL}
1	Neonate	Infant	2.01
2	Neonate	Toddler	1.76
3	Neonate	Child	1.14
4	Neonate	Adolescent	1.16
5	Infant	Toddler	0.2
6	Infant	Child	0.37
7	Infant	Adolescent	0.3
8	Toddler	Child	0.9
9	Toddler	Adolescent	0.6
10	Child	Adolescent	0.54

Table 5. *Estimated EXP_{CL} for the combinations of one pediatric dataset and one adult dataset in the analysis grouped by the FDA guidance*

No	Dataset 1	Dataset 2	EXP_{CL}
A	Newborn	Adult	1.15
B	Infant	Adult	0.61
C	Child	Adult	0.69
D	Adolescent	Adult	0.8

In all models of the analysis, the diagnostic plots of the observed concentrations versus population predicted concentrations shown adequate model fitting for each of the two combined datasets, although some of the bias existed in the combinations which had the infant dataset in the analysis grouped by the study population (***Figure 1***, ***Figure 2***, ***Figure3***).

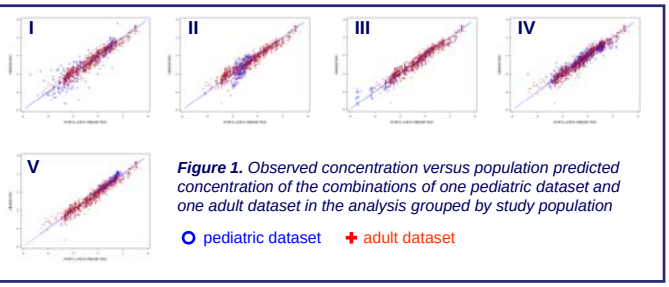

Figure 1. *Observed concentration versus population predicted concentration of the combinations of one pediatric dataset and one adult dataset in the analysis grouped by study population*

pediatric dataset adult dataset

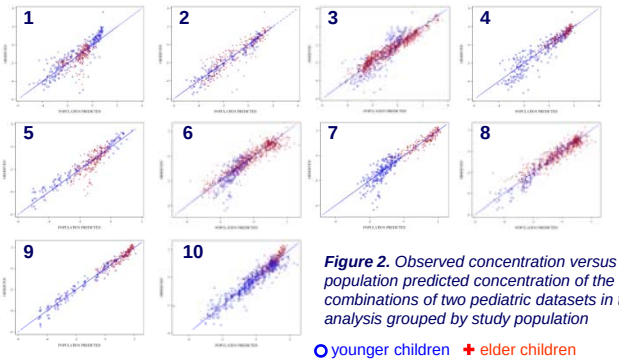

Figure 2. *Observed concentration versus population predicted concentration of the combinations of two pediatric datasets in the analysis grouped by study population*

younger children elder children

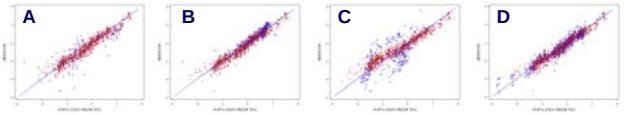

Figure 3. *Observed concentration versus population predicted concentration of the combinations of one pediatric dataset and one adult dataset in the analysis grouped by the FDA guidance*

pediatric dataset adult dataset

Conclusions

When scaling propofol clearance from adults to neonates, the allometric scaling exponent is above 1.

When scaling propofol clearance from adults to any pediatric dataset other than neonates, the scaling exponent varies between 0.57 and 0.81.

When scaling propofol clearance between pediatric datasets, the scaling exponent varies between 0.2 to 2.

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