Population PK modeling of Midazolam in Children
The effect of age versus other covariates

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Background & Aim

In order to develop rational dosing schemes for drugs in children, we investigate the influence of age-related changes on the PK and PD of drugs. For the ontogeny of the CYP3A subfamily, we use midazolam as an *in vivo* probe to describe the clearance of CYP3A substrates in different patient populations, ranging from neonates to adolescents.

The aim of the current analysis is to study, among other covariates, the influence of age-related changes on the clearance of midazolam in two paediatric populations.

Table 1. *Patient characteristics of dataset study 1 [1] and dataset study 2 [2]*

	study 1	*study 2*
Study population	**Postoperative**	**Critically ill**
	Elective craniofacial surgery	
Number of individuals	23	21
Total PK samples	198	260
Age (median, range)	11.2 m (3 – 25)	30 m (0.03 – 204)
Weight (median, range)	9.6 kg (5.1 – 12)	13 kg (2.8– 60)
PELOD score (median, range)	0 (0- 10)	10 (0 – 22)
Midazolam Administration	iv bolus: 0.1 mg/kg	iv bolus: 0.1 mg/kg
	iv infusion: 0.1 mg/kg/hr	iv infusion: 0.1mg/kg/hr
Max. duration infusion	22 hr	up to 627 hr

Methods

Two previously published studies on paediatric midazolam PK [1] [2] were merged in R and population PK modeling was performed using NONMEM 6.2. During the covariate analysis step, the influence of the study population (study factor), postnatal age, bodyweight (BW), gender, and severity of illness (PELOD score) on clearance were investigated.

[1] Peeters, M.Y. et al. (2006) Anesthesiology 104 (3), 466-4743

[2] de Wildt, S.N. et al. (2003) Crit Care Med 31 (7), 1952-1958

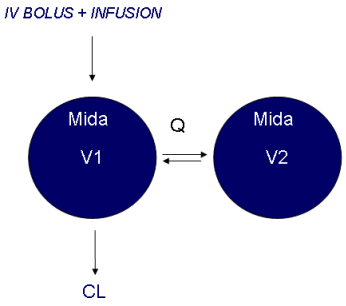
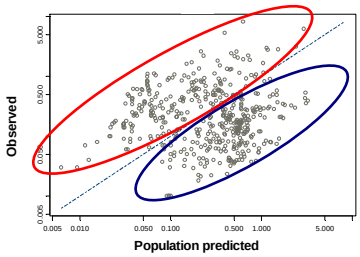


Figure 1. *Schematic representation of the PK model. Mida = midazolam*

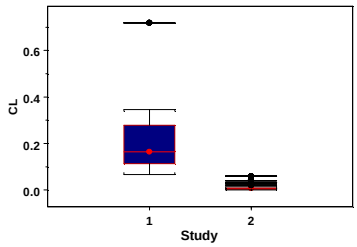
Results

Using a 2 compartment PK model (figure 1), the simple model of the combined dataset without covariates (figure 2A) showed remarkable differences in clearance between the postoperative [1] and critically ill [2] children (figure 2B). The influence of bodyweight on clearance seemed to vary considerably between the two study populations (figure 2C).

2A **Simple model: Diagnostics**



2B **Simple model: Influence of study factor**



2C **Simple model: Influence of bodyweight**

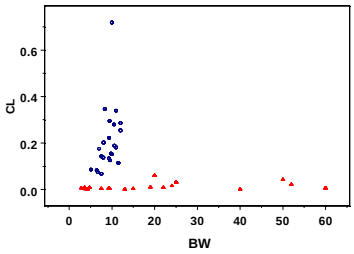


Figure 2. *Simple model: 2A: diagnostic plot of population predicted versus observed concentrations; 2B: difference in clearance (L/hr) between the two study groups (study 1 and 2); 2C: Bodyweight (kg) versus clearance (L/hr) (2C). Colors: blue = study 1, red = study 2.*

In the covariate analysis, a study factor added to clearance (table 2), as well as bodyweight as a covariate for clearance of midazolam for each of the two patient groups (table 2), all proved to significantly improve the model (figure 3, table 3). Clearance of midazolam was found to be reduced by 93% in critically ill children compared to postoperative children. The influence of bodyweight was linear in postoperative children, whereas an exponential scaling factor of 0.48 was found in critically ill children (table 3). Age and PELOD score were less predictive covariates for clearance compared to study factor and bodyweight.

3 **Covariate model: Diagnostics**

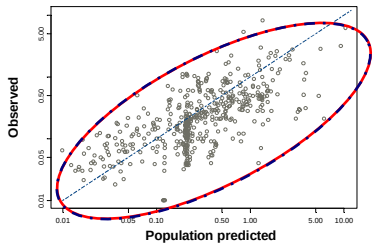


Figure 3. *Covariate model: diagnostic plot of population predicted versus observed concentrations. Colors: blue = study 1, red = study 2.*

Table 2. *Covariate model*

Study factor on clearance

IF (STUDY.EQ.1) TVCL=THETA(1)

IF (STUDY.EQ.2) TVCL=THETA(1)(1-THETA(2))*

Bodyweight on clearance in study 1

$TVCL*(BW/BW_{median})**THETA(3)$

Bodyweight on clearance in study 2

$TVCL*(BW/BW_{median})**THETA(4)$

Table 3. *Parameter values of the Covariate model.*

Parameter	*Value*	*CV(%)*	*LLCI*	*ULCI*
Fixed Effects				
Cl (L/hr)	0.113	11.9	0.0867	0.139
V_1 (L)	0.647	33.1	0.228	1.07
Q_{eq} (L/hr)	0.0423	17.4	0.0279	0.0567
V_2 (L)	4.62	1.3	3.05	6.19
Φ (study factor Cl)	0.932	1.89	0.898	0.966
Φ (exponent BW study 1)	0.99	29.7	0.414	1.57
Φ (exponent BW study 2)	0.484	44.6	0.0606	0.907
Interindividual Variability				
ω^2 (Cl)	0.398	38.4	0.0981	0.698
Residual error				
σ^2 (proportional)	0.493	11.2	0.385	0.601

Conclusion & Perspectives

In pediatric pharmacology, the emphasis is usually on the age-related influence on PK parameters. We show here that, similar to the adult population, other covariates (e.g. health state) should be quantified as well. More datasets including metabolites will be added to the PK and PD analysis, which will be followed by validation procedures, after which specific dosing guidelines will be developed.

TI PHARMA

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