Population PK of midazolam from preterm neonates to adults: a maturation model

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Background & Aim

In this analysis we aimed to develop a maturation model for the CYP3A4/5 enzyme activity using midazolam clearance as *in vivo* probe for preterm neonates from 26 weeks gestational age (GA) onwards to adults.

[1] de Wildt SN et al., Clin Pharmacol Ther. 2001 Dec;70(6):525-31
[2] Jacqz-Aigrain E et al,. Lancet. 1994 Sep 3;344(8923):646-50
[3] Peeters, M.Y. et al. (2006) Anesthesiology 104 (3), 466-474
[4] de Wildt, S.N. et al. (2003) Crit Care Med 31 (7), 1952-1958
[5] de Wildt SN et al (2000) Clin Pharmacol Ther 67:104.
[6] van Gerven JM et al., Br J Clin Pharmacol. 1997 Nov;44(5):487-93
[7] PAGE 19 (2010) Abstr 1819 [www.page-meeting.org/?abstract=1819]

Methods

Table 1. *Overview of the datasets used to develop the midazolam PK model.*

Dataset	de Wildt SN *et al.* (2001) [1]	Jacqz-Aigrain E. *et al.* (1994) [2]	Peeters, M.Y. *et al.* (2006) [3]	de Wildt SN *et al.* (2003) [4]	de Wildt SN *et al.* (2000) [5]	van Gerven J.M.A. *et al.* (1997) [6]
Patient Population	Preterm neonates	Preterm neonates with RDS syndrome*	Children after elective major craniofacial surgery	Pediatric intensive care patients	Oncology patients	Male adults
Indication for midazolam sedation	Sedation for invasive procedure in intensive care	Mechanical ventilation in intensive care	Postoperative sedation	Conscious sedation in intensive care	Sedation for invasive procedure	Healthy volunteers
Number of Patients	23	24	23	18	18	20
Midazolam Dose *median (range)*	0.1 mg/kg iv infusion in 30 minutes	60 µg/kg/hr iv infusion If GA < 33w → after t > 24hr 30 µg/kg/hr	0.1 mg/kg iv loading dose, 0.05-0.2 mg/kg/hr infusion	0.1 mg/kg loading dose, 0.05-0.4 mg/kg/hr infusion	0.1 (0.03-0.53) mg/kg iv bolus dose	0.1 mg/kg iv infusion in 20 minutes
Postnatal Age (PNA) *median (range)*	5 days (2.9-11)	0 days (0-1)	11.5 months (3.2 - 24.7)	38.5 months (0.03-203.5)	6.1 years (3.2 – 16.2)	24 years (20-31)
Gestational Age (GA) *median (range)*	28.3 weeks (26-33.6)	32 weeks (26-37)	-	-	-	-
Bodyweight in kg *median (range)*	1.07 (0.77-1.6)	1.64 (0.96-3.7)	9.6 (5.1– 12)	14 (2.8-60)	22.5 (12.6– 60.1)	50.4 (33.5-81)
PELOD Score *median (range)*	-	-	0 (0– 10)	0 (0-22)	0 (0)	0 (0)
Mechanical ventilation *N/ N_{TOTAL}*	12 / 23	24 / 24	2 / 23	15 / 18	0 / 18	0 / 20
Number of Samples	141	63	198	233	82	336

Pharmacokinetic data after IV midazolam administration were obtained from 6 previously reported studies (Table 1). Population PK modeling was performed with a two compartment model using NONMEM v6.2. In a systematic covariate analysis, the influence of postnatal age, gestational age, postmenstrual age, body weight (BW) and PELOD score (organ failure) was investigated.

Results

Upon inclusion of preterm neonate datasets, BW proved a significant covariate for clearance. The influence of BW was best described using an allometric equation (Equation 1) with a BW-dependent maturational exponent (BWME). BWME gradually changed from 0.91 in preterm neonates to 0.50 in adults, with Coeff1 of 0.88 (7.6%) and exp2 of – 0.128 (30.8%) (Table 2). BW was also linearly correlated with V1, and in an allometric equation with V2 with an exponent of 0.78. Clearance was reduced by 93% in ICU patients.[7] A 5.8 fold increase in V2 was estimated in patients after major craniofacial surgery.

$$CL_{TV} \times \left(\frac{BW_i}{BW_{mean}} \right)^{BWME}$$

$$BWME = Coeff_1 \times BW^{\exp 2}$$

Equation 1. *Allometric equation with an exponent that varies with bodyweight. Cl_{TV} : typical value for clearance, BW : body weight, BWME : BW-dependent maturational exponent , $Coeff_1$: coefficient of the exponential function, exp_2 : additional exponent of the allometric function.*

Table 2. *Population parameter estimates of the PK model in children (Figure 1).*

Parameter	Model fit Value	(CV%)	Bootstrap results Value	(CV%)
$Cl_{non\text{-}icu\ patients}$ (L/min/kg^{exp3})	0.12	(4.8)	0.12	(11.5)
$fCl_{non\text{-}icu\ patients}$ (L/min/kg^{exp3})	0.07	FIXED	0.07	FIXED
V_1 (L/kg)	1.77	(25.8)	1.85	(19.3)
V_2 (L/kg^{exp3})	4.27	(7.6)	4.25	(8.3)
$fV_{2\ children\ after\ elective\ major\ craniofacial\ surgery}$ (L/kg^{exp3})	5.83	(23)	6.3	(17.7)
Q (L/min)	0.68	(18)	0.68	(19.2)
$Coeff_{1\ (coefficient\ of\ the\ exponential\ function\ (equation\ 1)}$	0.88	(7.6)	0.89	(12.1)
$Exp_{2\ (additional\ exponent\ of\ the\ allometric\ function\ (equation\ 1)}$	-0.128	(30.8)	-0.128	(43.5)
$Exp3_{\ (allometric\ exponent\ of\ V2)}$	0.78	(8.9)	0.79	(8.7)
ω^2 (Cl)	0.39	(17.4)	0.36	(18.0)
ω^2 (V_1)	0.62	(52)	0.57	(40.8)
ω^2 (V_2)	0.44	(32.9)	0.42	(33.0)
ω^2 (V_2-V_1)	0.47	(43.6)	0.43	(43.4)
$\sigma^2_{proportional}$	0.12	(14.8)	0.11	(13.7)

ICU = intensitve care unit, $fCl_{non\text{-}icu\ patients}$

Post hoc Estimates Final model

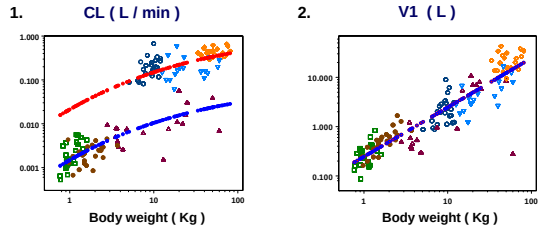


Figure 2. (1-4)

Covariate plots in final model, for bodyweight versus PK parameters CYP3A4/5 mediated clearance (CL), central (V1) volume of distrubution (1-2), and versus their ETA values (3-4).

Dotted lines: Population predicted post-hoc values of

- *: icu treatment group*
- *: non-icu treatment group.*

Table 3. *Legend for Figures 2 and 3.*

Green:	Preterm neonates [1]
Brown:	Preterm neonates with RDS syndrome [2]
Dark blue:	Children after elective major craniofacial surgery [3]
Red:	Pediatric intensive care patients patients [4]
Light blue:	Oncology patients [5]
Orange:	Male adults [6]

Observed Concentration vs Population Predicted Concentration In Final Model

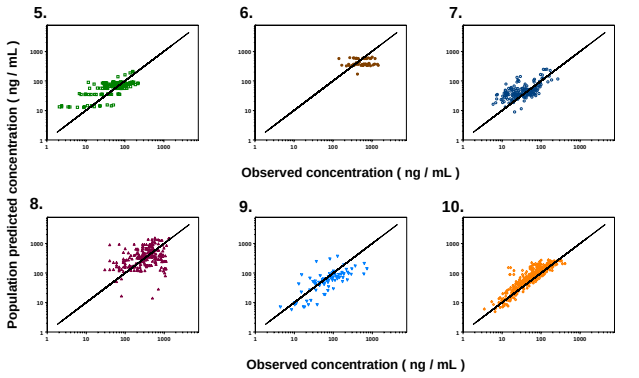
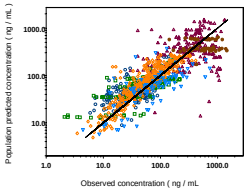


Figure 3. (5-10)

Visual diagnostics plots of each dataset of final model. Observed concentrations versus predicted concentrations by the model (PRED) for midazolam. Below: the overall diagnostics of the combined data.



Conclusion & Perspectives

A maturation model for midazolam clearance from preterm neonates to adults has been developed for both ICU as well as non-ICU treatment patients, showing that CYP3A4/5 activity matures in (preterm) neonates up to 5-10 kg of body weight. Thereafter, maturation slows down resulting in minimal increase between 10 and 81 kg of body weight.

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TI PHARMA

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