A Pharmacokinetic Model for Dexmedetomidine in Children and Adults

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MEDICAL AND HEALTH SCIENCES

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Dexmedetomidine

- Dexmedetomidine is an α_2-agonist with sedative, analgesic and anxiolytic properties
- Used for intravenous sedation in the intensive care unit and as an anaesthetic adjunct
- Dexmedetomidine PK have been described for discrete cohorts: children, healthy adult volunteers and obese adults
- This study sought to develop a dexmedetomidine PK model, applicable to individuals of a broad range of ages and weights, including obese adults

Hannivoort LN, Eleveld DJ, Proost JH, *et al.* Development of an Optimized Pharmacokinetic Model of Dexmedetomidine Using Target-controlled Infusion in Healthy Volunteers. *Anesthesiology* 2015; 123: 357-367.

Data sources

Study	Median (range)		
	Age	Weight (kg)	BMI (kg/m²)
Hannivoort (N=18)	41.4 years (18-68.8 years)	69.6 (53.9-94.1)	23.7 (18.3-29.3)
Potts (N=95)	3.5 years (40 PMAW-14.6 years)	14.2 (3.1-58.9)	16.1 (9.9-25.2)
Cortinez (N=40)	35 years (18-60 years)	94 (59.2-152)	35.9 (22.5-51.6)
Rolle (N=40)	44 years (23-59 years)	89 (47-126)	35.5 (18.8-46.9)
Talke (N=10)	32 years (21-36 years)	79 (52-89)	24.8 (20.3-27.1)

Rolle A, Paredes S, Cortinez LI, *et al.* Dexmedetomidine metabolic clearance is not affected by fat mass in obese patients. *Br J Anaesth* 2018; 120: 969-977.

Hannivoort LN, Eleveld DJ, Proost JH, *et al.* Development of an Optimized Pharmacokinetic Model of Dexmedetomidine Using Target-controlled Infusion in Healthy Volunteers. *Anesthesiology* 2015; 123: 357-367.

Potts AL, Warman GR, Anderson BJ. Dexmedetomidine disposition in children: a population analysis. *Pediatric Anesthesia* 2008; 18: 722-730.
Potts AL, Anderson BJ, Holford NH, *et al.* Dexmedetomidine hemodynamics in children after cardiac surgery. *Paediatr Anaesth* 2010; 20: 425-33.
Cortinez LI, Anderson BJ, Holford NH, *et al.* Dexmedetomidine pharmacokinetics in the obese. *Eur J Clin Pharmacol* 2010; 71: 1501-1508. 4

Pharmacokinetic analyses

- Two and three-compartment structural models with first order elimination were tested to describe dexmedetomidine PK after an intravenous infusion
- Models were parameterised in terms of clearance (CL), volume of distribution (V), and intercompartmental clearance (Q)
- PK parameters were scaled using allometric theory (allometric exponents fixed at 1 for V and ¾ for CL)
- Population parameter variability (PPV) was accounted for using an exponential model for the random effect variables (η)
- Residual unidentified variability (RUV) was modelled using both proportional and additive residual errors

Covariate analyses for age and size

- The influence of body composition on dexmedetomidine PK was tested using total body weight (TBW), fat-free mass (FFM) and normal fat mass (NFM)

$$NFM = FFM + Ffat \times (TBM - FFM)$$

$$CL_{Child} = CL_{STD} \times \left(\frac{NFM_{Child}}{NFM_{STD}}\right)^{3/4}$$

- The maturation of dexmedetomidine CL was described using a maturation function

$$MF = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

Al-Sallami, H.S.; Goulding, A.; Grant, A.; Taylor, R.; Holford, N.; Duffull, S.B. Prediction of Fat-Free Mass in Children. *Clin. Pharmacokinet.* **2015**, *54*, 1169–1178.

Pharmacokinetic parameter estimates

Parameter	Estimate	PPV (%)	95%CI	Sh%
V1 (L/70 kg)	25.2	103.9	20.9, 31.3	16.4
V2 (L/70kg)	34.4	41.8	24.3, 44.2	15.5
V3 (L/70 kg)	65.4	61.6	53.4, 74.5	8.4
CL (L/min/70 kg)	0.897	35.8	0.81, 1.02	4.1
Q2 (L/min/70kg)	1.68	63.2	1.22, 1.97	12.5
Q3 (L/min/70 kg)	0.62	89.7	0.45, 0.83	21.4
FFATV	0.293	-	0.13, 0.55	-
FFATCL	0 FIX	-	-	-
TM_{50}	52.4	-	43.5, 68.8	-
Hill	1 FIX	-	-	-
Additive Residual Error (µg/mL)	0.004	η_{RUV} 0.32	-	
Proportional Residual Error (%)	0.19	-	0.18, 0.20	

Morse, J.D.; Cortinez, L.I.; Anderson, B.J. A Universal Pharmacokinetic Model for Dexmedetomidine in Children and Adults. *Journal of clinical medicine* 2020, *9*, doi:10.3390/jcm9113480.

Maturation of dexmedetomidine CL with FFM

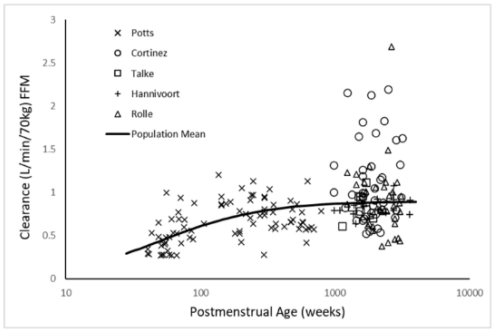

Figure 1: Maturation of dexmedetomidine clearance in the pooled dataset when scaled using fat free mass.

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Dexmedetomidine pcVPC

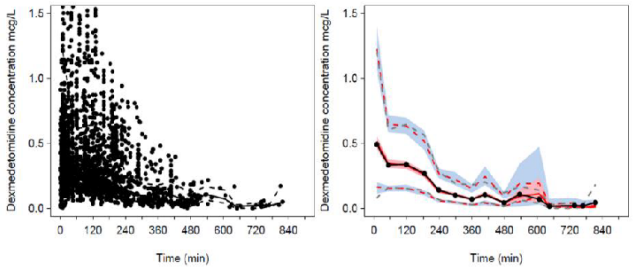

Figure 2: Prediction-corrected visual predictive check (pc-VPC) for the universal dexmedetomidine PK model. Plots show median (solid) and 90% intervals (dashed lines). The left-hand plot shows all prediction-corrected observed dexmedetomidine concentrations. Right-hand plot shows prediction-corrected percentiles (10%, 50%, and 90%) for observations (grey dashed lines) and predictions (red dashed lines) with 95% confidence intervals for prediction percentiles (median, pink shading; 5th and 95th blue shading).

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Discussion

- We have derived a universal population PK model for dexmedetomidine that is applicable to both children and adults with a wide range of weights
- FFM was a better size descriptor than TBW for CL and NFM (FFAT=0.293) was the most suitable size descriptor to describe dexmedetomidine changes in volumes of distribution
- This parameter set could be programmed into target-controlled infusion pumps for use in a broad population

Acknowledgments

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