Dexmedetomidine Pharmacokinetics and a New Dosing Paradigm in Infants Supported With Cardiopulmonary Bypass

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Background

- Dexmedetomidine (DMET) is increasingly used off-label in infants and children with cardiac disease during cardiopulmonary bypass (CPB) and in the postoperative period.
- CPB involves induced hypothermia, hemodilution of albumin, altered blood flow to target organs, potential adsorption of drug by CPB circuit materials, and marked inflammation
- Dosing of DMET during CPB is expected to differ from dosing in those not supported with CPB

Objectives

- Characterize the effect of CPB on dexmedetomidine clearance (CL) and volume of distribution (V) in infants and young children
- Characterize safety events and sedation scores
- Identify preliminary dosing recommendations during CPB

Methods

Study Design

•Open-label, single-center, opportunistic PK and safety study of in patients ≤ 36 months of age administered dexmedetomidine per standard of care via continuous infusion

•Blood sampling at specified time intervals before, during, and after CPB

•Collection of sedation scores and safety events (bradycardia, hypotension)

•High-performance liquid chromatography tandem mass spectrometry after solid phase extraction (University of Turku, Finland) to determine plasma concentrations

Pharmacokinetic Analyses

•Nonlinear mixed effects modeling with NONMEM® (version 7.2, Icon Solutions, Ellicott City, MD) using base model from historical patients

•Investigation of CPB-related factors and fixed effects as covariates

•Numeric comparison of final model-estimated PK parameters to those from historical patients (population CL in historic patients: 42.1 L/h/70 kg)

•Simulation of dosing for a typical neonate and infant using the final model.

Results

Table 1. Participant characteristics

	N=18
Age (months)*	3.3 (0.1, 34.0)
White race (N, %)	11 (61)
Male (N, %)	8 (50)
Duration of CPB (min)*	161 (63, 394)
DMET starting dose (mcg/kg/min)*	0.5 (0.5-0.8)
Samples per participant*	10 (4-14)

*median (range)

Table 2. Final two-compartment model

$$CL_i = \{[CL * (\text{pre}_{\text{CPB}} + \text{post}_{\text{CPB}})] + [CL_{onCPB} * on_{CPB}]\} * \left(\frac{WT_i}{70\ kg}\right)^{0.75} * \left(\frac{PMA_i^{Hill}}{TM_{50}^{Hill} + PMA_i^{Hill}}\right) * e^{\eta CLi}$$

$$Vc_i = Vc * \left(\frac{WT_i}{70\ kg}\right)^{1} * F_{inf} * e^{\eta Vci}$$

$$Q_i = \{[Q * (\text{pre}_{\text{CPB}} + \text{post}_{\text{CPB}})] + \left[Q * \left(\frac{CL_{onCPB}}{CL_{std}}\right) * \text{on}_{\text{CPB}}\right]\} * \left(\frac{WT_i}{70\ kg}\right)^{0.75}$$

$$Vp_i = Vp * \left(\frac{WT_i}{70\ kg}\right)^{1}$$

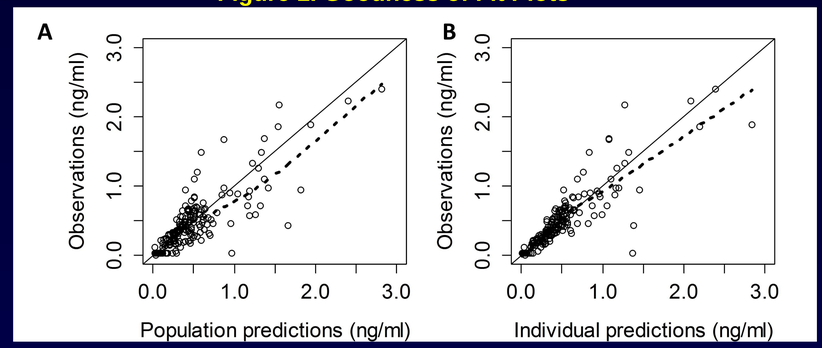
$$Vss_i = Vp_i + Vc_i$$

Table 3. Final Model Parameter Estimates

Parameter	Estimate	RSE (%)	Bootstrap CI		
			2.5%	Median	97.5%
Structural PK Model					
$CL_{pre\_postCPB}$ (L/h, 70 kg)	42.1				
CL_{onCPB} (L/h, 70 kg)	13.4	41	3.58	13.70	27.15
$Q_{pre\_post\_CPB}$ (L/h, 70 kg)	78.3				
Vc (L, 70 kg)	56.3				
Vp (L, 70 kg)	69				
Hill coefficient	2.56				
TM50 (weeks)	44.5				
F_{inf}	4.94	22	3.65	4.96	7.24
Inter-individual Variability (%CV)					
CL IIV	41.8	39	20.30	42.28	57.03
Vc IIV	51.0	57	27.26	51.02	75.85
Residual Variability					
Proportional error (%)	31.6	18	26.16	32.02	39.25
Additive error (ng/ml)	0.03	54	0.013	0.030	0.046

Results

Figure 1. Goodness of Fit Plots



- The final model described the data well with precise parameter estimates
- Eight of the 18 participants (44%) developed study-defined hypotension in the postoperative period.
- Three of the 18 participants (18%) had bradycardia

Table 4. Preliminary Dosing Recommendations

Phase of CPB	Postmenstrual age (weeks)	
	42	92
Loading dose (µg/kg)	0.7	0.7
Maintenance pre-CPB (µg/kg/h)	0.7	0.8
Maintenance: on CPB (µg/kg/h)	0.2	0.25
Maintenance: post-CPB (µg/kg/h)	0.4	0.6

Conclusions

- We identified markedly decreased CL and increased V during CPB compared to estimates from historical infants and children who had DMET initiated in the peri-surgical or procedural periods.
- DMET was well tolerated in our cohort
- Our study suggests a loading dose is necessary, followed by maintenance dosing that varies depending on participant PMA and whether the participant is pre-, on, or post-CPB to achieve therapeutic concentrations prior to initiation of CPB.

References

Chrysostomou C, Di Filippo S, Manrique AM, et al. Use of dexmedetomidine in children after cardiac and thoracic surgery. Pediatr Crit Care Med. 2006;7:126–131.

Potts AL, Warman GR, Anderson BJ. Dexmedetomidine disposition in children: a population analysis. Pediatr Anesth. 2008;18:722–730.

Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. Intensive Care Med. 2010;36:2109–2116.

Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. Clin Pharmacokinet. 2003;42:403–417..

Disclosures

www.dcri.duke.edu/research/coi.jsp