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Dexmedetomidine Pharmacology in Neonates and Infants After Open Heart Surgery

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BACKGROUND: Dexmedetomidine is a highly selective α_2-agonist with hypnotic, analgesic, and anxiolytic properties. Despite off-label administration, dexmedetomidine has found a niche in critically ill neonates and infants with congenital heart disease because of its minimal effects on respiratory function at sedative doses, facilitating early extubation and fast-track postoperative care. There are little pharmacokinetic data regarding newborns who have immature drug metabolizing capacity and who are at risk for reduced dexmedetomidine clearance and drug toxicity. The aim of this study was to determine the pharmacokinetics of dexmedetomidine in neonates and infants after open heart surgery. This study included 23 evaluable neonates (age, 1 day–1 month) and 36 evaluable infants (age, 1 month–24 months) after open heart surgery.

METHODS: Full-term neonates and infants requiring mechanical ventilation after open heart surgery received dexmedetomidine in a dose-escalation study. Dexmedetomidine was administered as a loading dose over 10 minutes followed by a continuous IV infusion up to 24 hours. Cohorts of 12 infants were enrolled sequentially to receive 0.35, 0.7, or 1 μg/kg dexmedetomidine followed by 0.25, 0.5, or 0.75 μg/kg/h dexmedetomidine, respectively. Cohorts of 9 neonates received 0.25, 0.35, or 0.5 μg/kg dexmedetomidine followed by 0.2, 0.3, or 0.4 μg/kg/h dexmedetomidine, respectively. Plasma dexmedetomidine concentrations were determined using a validated high-performance liquid chromatography-tandem mass spectrometry assay. A population nonlinear mixed effects modeling approach was used to characterize dexmedetomidine pharmacokinetics.

RESULTS: Pharmacokinetic parameters of dexmedetomidine were estimated using a 2-compartment disposition model with weight allometrically scaled as a covariate on drug clearance, intercompartmental clearance, central and peripheral volume of distributions and age, total bypass time, and intracardiac shunting on clearance. Dexmedetomidine demonstrated a plasma drug clearance of $657 \times (\text{weight}/70)^{0.75}$ mL/min, intercompartmental clearance of $6780 \times (\text{weight}/70)^{0.75}$ mL/min, central volume of distribution of $88 \times (\text{weight}/70)$ L and peripheral volume of distribution of $112 \times (\text{weight}/70)$ L for a typical subject with age >1 month with a cardiopulmonary bypass time of 60 minutes and without right-to-left intracardiac shunt. Dexmedetomidine pharmacokinetics may be influenced by age during the neonatal period, weight, total bypass time, and presence of intracardiac shunt.

CONCLUSIONS: Dexmedetomidine clearance is significantly diminished in full-term newborns and increases rapidly in the first few weeks of life. The dependence of clearance on age during the first few weeks of life reflects the relative immaturity of metabolic processes during the newborn period. Continuous infusions of up to 0.3 μg/kg/h in neonates and 0.75 μg/kg/h in infants were well tolerated after open heart surgery. (Anesth Analg 2016;122:1556–66)

Dexmedetomidine is a highly selective α_2-agonist with sedative and analgesic properties. Currently, it is Food and Drug Administration (FDA)-approved for sedation in the initially intubated and mechanically ventilated adult patients in an intensive care unit (ICU) setting and for procedural sedation of nonintubated adult patients, for a maximum of 24 hours. Despite off-label administration, dexmedetomidine has found a niche in pediatric critically ill patients, particularly in those with congenital heart disease. In more recent years, early tracheal extubation and fast-track postoperative care in congenital heart disease has gained increasing support.[1–3] Dexmedetomidine is being used in this setting because of its minimal effects on respiratory function at sedative doses. In addition to providing sedation after open heart surgery, published reports of dexmedetomidine administration include intraoperative adjunctive medication for anesthesia, facilitation of cardiac catheterization, treatment of substance withdrawal symptoms, and treatment of tachyarrhythmias in patients with congenital heart disease.[4–10]

Although use in pediatric ICUs is widespread, limited pediatric pharmacokinetic (PK) data are available in neonates and infants. It is well recognized that newborns have immature metabolic capacity for many medications.[11–15]

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Table 1. Dexmedetomidine Dose Escalation Scheme

Infants (age 1–24 mo)			Neonates (age < 1 mo)					
			Planned enrollment			Actual enrollment		
Cohort	Loading dose (μg/kg)	Infusion rate (μg/kg/h)	Cohort	Loading dose (μg/kg)	Infusion rate (μg/kg/h)	Cohort	Loading dose (μg/kg)	Infusion rate (μg/kg/h)
1 (*n* = 12)	0.35	0.25	4 (*n* = 9)	0.25	0.2	4 (*n* = 9)	0.25	0.2
2 (*n* = 12)	0.7	0.5	5 (*n* = 9)	0.5	0.4	4A (*n* = 9)	0.35	0.3
3 (*n* = 12)	1	0.75	6 (*n* = 9)	0.75	0.6	5 (*n* = 5)	0.5	0.4

Dexmedetomidine is extensively metabolized in the liver by direct glucuronidation by uridine 5′-diphosphate-glucuronosyltransferases (UGTs) and cytochrome P450 CYP2A6-mediated aliphatic hydroxylation. The impact of immature drug-metabolizing enzyme systems, altered physiology, and intraoperative procedures such as cardiopulmonary bypass (CPB) on dexmedetomidine drug disposition has not been well studied in neonates (age, 0–1 month). More specific to neonates, the immature drug-metabolizing enzyme systems during the newborn period may result in reduced dexmedetomidine clearance and potential for drug toxicity at doses more commonly administered to infants and older children. We previously reported the pharmacokinetics and safety and pharmacodynamics of dexmedetomidine administered to infants (age 1 month–24 months) after open heart surgery.[16,17] We now present PK and safety data of dexmedetomidine administered to neonates with congenital heart disease after open heart surgery in combination with the PK data from the previously reported infant population, also after open heart surgery.

METHODS

Clinical Trial

This study was conducted with the FDA under the investigational new drug (IND) application (#69,758). After IRB approval and written informed parental consent, full-term neonates and infants with congenital heart disease undergoing open heart surgery with adequate hepatic and renal function and without evidence of heart block were eligible for enrollment. Subjects were planned to be enrolled in a dose-escalation trial of an IV loading dose followed by a continuous IV infusion (CIVI) of dexmedetomidine as presented in Table 1. Doses were chosen to cover the range of doses currently included in the drug monograph.

Dexmedetomidine was initiated in the cardiac intensive care unit within 3 hours of arrival from the operating room, with the loading dose administered over 10 minutes followed by a CIVI of 4 to 24 hours per the clinical team providing direct care for the child. Twelve evaluable subjects were enrolled in each infant cohort. The initial study design planned for the enrollment of 9 evaluable subjects in each neonatal cohort. Interim PK and safety analyses were performed at the completion of each dosing cohort and reviewed by the FDA before enrollment to the next higher dose. Infant enrollment and analysis were completed before the initiation of the neonatal trial.

Pharmacokinetic Sampling and Drug Quantitation

PK samples consisted of 1 mL of blood. Infant and neonatal PK sampling times are represented in Table 2. PK sampling did not exceed 3 mL/kg for any subject. Plasma was separated by centrifugation and stored at −80°C. Dexmedetomidine plasma concentrations were determined using a validated high-performance liquid chromatography-tandem mass spectrometry assay adapted from previously described methodology, with a lower limit of quantitation of 5 pg/mL.[18]

Pharmacostatistical Analysis

Nonlinear Mixed Effects Pharmacokinetic Modeling

The population PK analysis was conducted using NONMEM (ICON Development Solutions, Ellicott City, MD) version VI, level 2.0 (ADVAN 3, TRANS 4). Dexemedetomidine plasma concentrations below the limit of quantitation were not included in the analysis. All models were run with the first-order conditional estimation with interaction method. S-Plus version 6.2 (Insightful, Inc., Data Analysis Products Division, Seattle, WA) was used for goodness-of-fit diagnostics and graphical displays. The goodness of fit from each NONMEM run was assessed by examining the following criteria: visual inspection of diagnostic scatter plots (observed versus predicted concentration, observed and predicted concentration versus time, and weighted residual versus predicted concentration or time), the precision of the parameter estimates as measured by asymptotic SEs derived from the covariance matrix of the estimates, successful minimization with at least 3 significant digits in parameter estimates, changes in the minimum value of the objective function (MVOF), and changes in the estimates of interindividual and residual variability for the specified model.

Base Model

One-, two-, and three-compartment models were investigated. A two-compartment disposition model was deemed optimal to define the dexmedetomidine plasma concentration profile based on the results from the model-building process (goodness-of-fit diagnostics as described earlier) and supported by previously published data.[16,19–21] Models were parameterized by clearance (CL, mL/min), intercompartmental clearance (Q, mL/min), central volume of distribution (V1, liters), and peripheral volume of distribution (V2, liters).

An exponential variance model was used to describe the unexplained random variability of PK parameters across individuals in the form: $P_i = \theta_k \exp(\eta_{ki})$, where P_i is the estimated parameter value for the individual subject i, θ_k is the typical population value of parameter k, and η_{ki} are the interindividual random effects for individual i and parameter k. Models were explored using various interindividual

Table 2. Infant and Neonatal PK Sampling

	Sampling times	Total blood volume (mL)
Infants		
Cohort 1	Before and after loading dose During infusion: 30 min, 6 h, 12 h, at EOI After EOI: 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h	14
Cohort 2 and 3	Before loading dose During infusion: 30 min, 1 h, 2 h, 4–6 h, EOI After EOI: 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 15–18 h	14
Neonates (kg)		
2.0–<2.5	During infusion: 15 min before EOI After EOI: 15 min, 30 min, 1 h, 4 h, 10 h	6
2.5–<3.0	During infusion: 15 min before EOI After EOI: 15 min, 30 min, 1 h, 2 h, 6 h, 12 h	7
3.0–<4.0	During infusion: 30 min, 6 h, 15 min before EOI After EOI: 15 min, 30 min, 1 h, 3 h, 9 h, 15 h	9
≥4.0	During infusion: 30 min, 4 h, 8 h, 15 min before EOI After EOI: 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 18 h	12

EOI = end of infusion; PK = pharmacokinetic.

random effect covariance structures. Interindividual variability was initially estimated for clearance and then subsequently for the remaining PK parameters.

Additive, proportional, and combined (additive and proportional) residual error models were considered during the model-building process. Ultimately, a combined additive and proportional error model was used to describe random residual variability: $C_{obs,ij} = (C_{pred,ij} \times (1 + \varepsilon_{ijP})) + \varepsilon_{ijA}$, where $C_{obs,ij}$ is the observed concentration j in individual i, $C_{pred,ij}$ is the individual predicted concentration, ε_{ijP} is the proportional residual random error, and ε_{ijA} is the additive residual random error for individual i and measurement j.

Full Covariate Model

A full covariate model was constructed to make inferences about the effects of covariates on dexmedetomidine disposition using the allometrically adjusted model. Covariate effects were predefined based on the clinical interest, previous knowledge, physiologic plausibility, and previous evaluation in the infant-only analysis. Contrary to stepwise hypothesis testing, the full model approach is advocated when the goal of the analysis is effect estimation and avoids the problem of selection bias, which is particularly problematic in small datasets.[22,23] The full model included effects of age, weight, total CPB time, and intracardiac shunting. Intracardiac shunting was defined as any cardiac anatomy that resulted in right-to-left shunting of blood with pulmonary blood flow to systemic blood flow ratio (Qp:Qs) of <1. The most common anatomy associated with intracardiac shunting in this study population was single ventricle physiology after stage 2 palliation, i.e., Glenn or hemi-Fontan procedure.

Age was incorporated as a covariate on clearance using an E_{max} model. The impact of weight on all PK parameters was investigated using an allometric model: $TVP = \theta_{TVP} \times (WT_i/WT_{ref})^{\theta allometric}$, where TVP is the typical value of a parameter and $\theta_{allometric}$ is an allometric power parameter based on the physiologic consideration of size impact on metabolic processes and is fixed at a value of 0.75 for clearances and a value of 1 for volumes.[24–27] A reference weight of 70 kg was used to allow for easy comparison with previous results in adult populations. Total CPB time was evaluated as a covariate on clearance using a power model normalized to the median total bypass time, based on the hypothesis that a longer bypass time would impair clearance immediately postoperatively. Finally, intracardiac shunting was evaluated as a dichotomous covariate on clearance, based on the hypothesis that the presence of an intracardiac shunt with a ratio of pulmonary blood flow to systemic blood flow (Q_p:Q_s) < 1 would result in higher systemic circulation and increased clearance because of dexmedetomidine's relatively high extraction ratio. Although a full model approach was advocated for inference about covariate effects themselves, a stepwise reduction of the full model was also performed to illustrate the individual contribution of each covariate effect to the overall goodness of fit.

Alternate Covariate Model

The impact of weight on all PK parameters was also investigated using a linear model: $TVP = \theta_{TVP} \times (WT_i/WT_{ref})$ using a reference weight of 70 kg. Age, total CPB time, and intracardiac shunt were evaluated as described earlier.

Model Evaluation

Log-likelihood profiling was performed for each of the estimated fixed effect parameters, in an effort to illustrate the marginal (approximate) −2 log-likelihood profile for each parameter. Assuming that the difference in −2 log-likelihood for nested models is χ^2 distributed, 95% confidence intervals were constructed by selecting fixed effect parameter values associated with a change of 3.84 points in the MVOF, when compared with the maximum likelihood estimate. It is acknowledged that the accuracy of these methods may be compromised under conditions when an approximation to the likelihood is required, but the purpose was simply to provide a relative comparison of parameter precision.

Simulations

The full covariate model was used to simulate expected concentration-time profiles under various dosing scenarios. Five hundred Monte Carlo simulation replicates of typical individuals at 3 different ages were performed, incorporating interindividual and residual random variability. A loading dose of 0.5 μg/kg followed by a continuous infusion of 0.4 μg/kg/h for 18 hours was simulated for the youngest, median, and oldest child without right-to-left intracardiac

Table 3. Subject Demographics and Baseline Characteristics

	Infants			Neonates			
	Cohort 1 (*n* = 12)	Cohort 2 (*n* = 12)	Cohort 3 (*n* = 12)	Cohort 4 (*n* = 9)	Cohort 4A (*n* = 9)	Cohort 5 (*n* = 5)	Overall
Age (mo)	9.3 (3.3–20.4)	7.8 (3.9–18.5)	7.2 (2.6–19.6)	0.1 (0.07–0.59)	0.1 (0.03–0.79)	0.13 (0.07–0.23)	4.3
Weight (kg)	7.5 (5.3–11.9)	7.0 (5.4–10.2)	6.9 (5.1–11.2)	3.5 (2.3–4.2)	3.2 (2.8–3.8)	3.4 (3.4–3.6)	5.9
Gender							
Female	5	6	5	6	3	2	27
Male	7	6	7	3	6	3	32
Intracardiac shunt							
Q_p:Q_s <1	5	7	7	0	0	0	19
Q_p:Q_s ≥1	7	5	5	9	5	9	40
CPB (min)	52.5 (16–70)	60 (24–99)	58 (28–169)	76 (52–106)	75 (49–109)	92 (60–141)	63
Dexmedetomidine duration (h)	6.9 (4.4–24)	8.8 (3.2–24)	8.8 (4.4–22.9)	22.8 (12.3–23.7)	22.9 (8.7–24.3)	16.5 (7.5–22.3)	10.1

Data presented as median (range).
CPB = cardiopulmonary bypass.

shunting (0.03 months and 2.8 kg, 4.3 months and 5.8 kg, 20.4 months and 11.9 kg). All subjects were simulated with the median bypass time of 60 minutes. Similarly, in our study, simulations were performed for the 3 neonates who experienced hypotension requiring cardiopulmonary resuscitation (CPR) and did not have plasma dexmedetomidine concentrations measured. The expected value for the typical individual was obtained by selecting the median plasma concentration-time profile across the simulation replicates.

Safety Monitoring

Dose limiting toxicities included bradycardia, hypotension, oversedation, prolonged sedation, or any serious adverse event possibly, probably, or definitely related to dexmedetomidine administration. Bradycardia was defined as heart rate <60 to 80 beats per minute, and hypotension was defined as mean arterial pressure <30 to 50 mm Hg (based on the age). Oversedation was any sedation resulting in clinically relevant symptoms, including difficult arousal with stimulation, bradycardia, hypotension, or bradypnea. Prolonged sedation was defined as clinical signs of ongoing sedation ≥4 hours after discontinuation of dexmedetomidine resulting in delayed tracheal extubation because of depth of sedation. The maximum tolerated dose (MTD) was defined as the highest dose cohort within each age group in which <3 subjects experienced a dose-limiting toxicity.

In addition, serial electrocardiograms (EKGs) were used to evaluate for evidence of cardiac ischemia after dexmedetomidine administration. Ischemia was defined as widened Q-waves (>0.035 seconds), new T-wave inversion, or ST-segment changes >2 mm from pretreatment EKG. Serial alanine aminotransferase (ALT) levels were measured to evaluate for evidence of hepatotoxicity (ALT > 3x upper limit of normal). Adrenal suppression was monitored based on clinical indicators, including electrolyte abnormalities and refractory hypotension. Ocular dryness was monitored by physical examination.

RESULTS

Dose Escalation

In the infant population, dose escalation occurred as initially planned. In the neonates, dose escalation was modified for safety concerns. The dose was escalated to cohort 5 (loading dose of 0.5 μg/kg and infusion of 0.4 μg/kg/h); however, it was determined that this dose exceeded the MTD because of the adverse event profile, and accrual to this dosing cohort was stopped with enrollment of only 5 evaluable subjects. The dose was then reduced, and dosing cohort 4A was subsequently studied, with a total of 9 evaluable subjects enrolled in this cohort, for a total of 23 neonates (Table 1).

Study Conduct

Sixty-eight subjects (38 infants and 30 neonates) were enrolled in this study to achieve a total of 59 evaluable subjects (36 infants and 23 neonates). Demographics of evaluable subjects are listed in Table 3. The median age and weight of the subjects were 4.3 months (1 day–20.4 months) and 5.97 kg (2.3–11.9 kg). Median duration of dexmedetomidine administration was 10.1 hours (3.2–24.3 hours). Two infants and 7 neonates were deemed inevaluable for the primary PK end point and were excluded from data analysis because of their clinical condition and early discontinuation of the infusion. One infant was found to have a peripheral IV catheter malfunction. One infant experienced hypotension and ongoing postoperative bleeding. Three neonates were removed from the study because of the need for surgical removal of mediastinal clots. Two other neonates experienced cardiopulmonary arrest attributed to cardiac tamponade. Two neonates experienced atrial ectopy.

Pharmacokinetic Analysis

Concentration-time profiles for each cohort are represented in Figure 1. The intraday and interday coefficients of variation were 0.74% to 6.67% and 0.67% to 4.86%, respectively, for dexmedetomidine concentrations in the range of 5 to 1200 pg/mL.

Base Model

All models were developed based on the data from the 59 subjects. Three percent of the neonatal PK samples and 8% of the infant PK samples were below the limit of quantitation and were not included in the analysis. The final structural model was a two-compartment disposition model with interindividual random effects estimated on CL, V1, Q, and V2 and covariance between CL, V1, and Q interindividual random effects. Using first-order conditional estimation

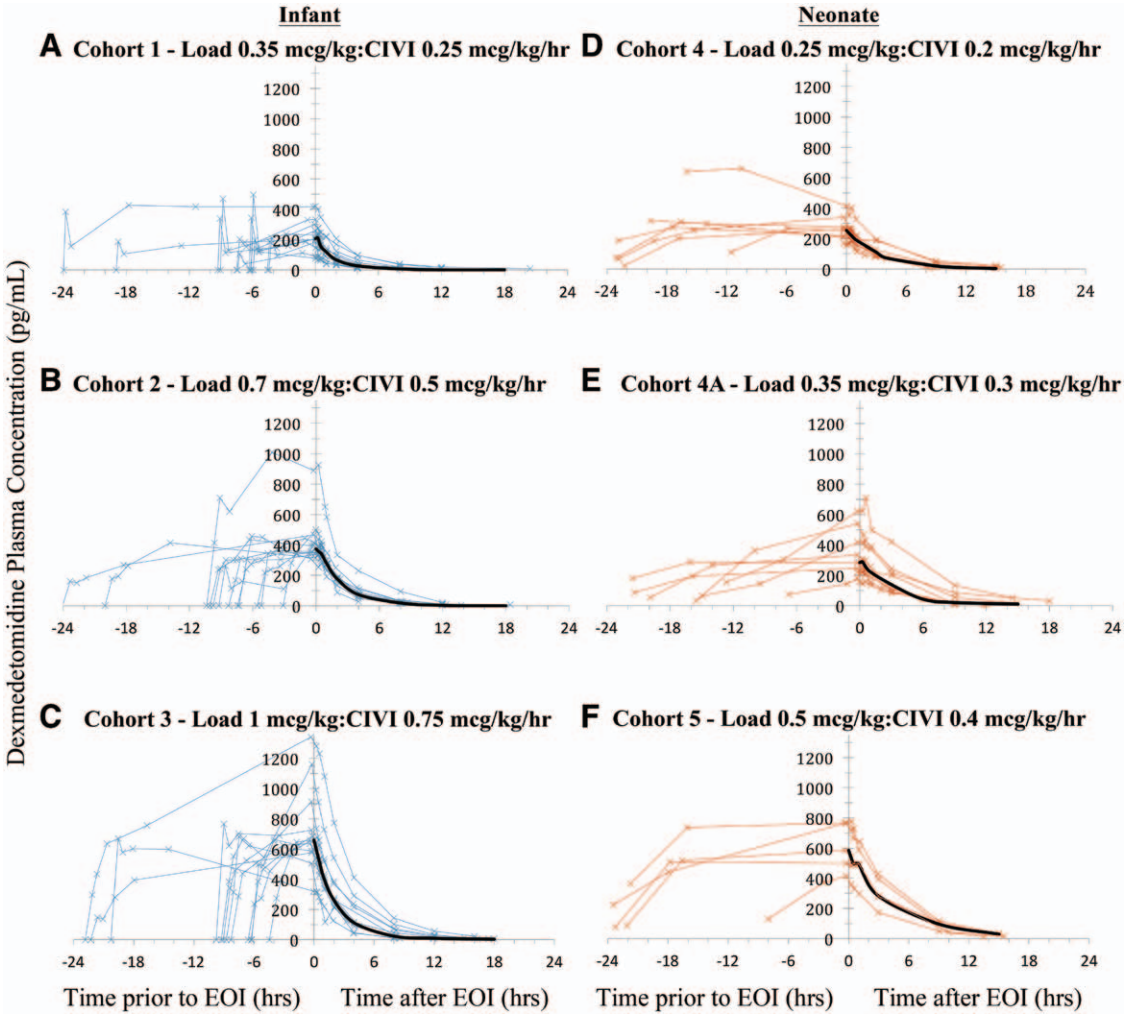

Figure 1. Observed concentration-time profiles for dexmedetomidine for each subject in all 6 dosing cohorts. Infant dosing cohorts are represented in blue (continuous IV infusion [CIVI] dose range, 0.25–0.75 μg/kg/h), with neonatal dosing cohorts represented in orange (CIVI dose range, 0.2–0.4 μg/kg/h). Median concentrations after end of infusion (EOI) are represented in black. Plasma concentrations obtained before and after EOI are shown. EOI occurs at 0 hours. Note that neonates in cohort 5 received approximately one-half of the dose as infants in cohort 3, yet achieved similar plasma concentrations.

with interaction estimation, the final model minimized with successful execution of the covariance step.

Full Covariate Model

Final parameter estimates and interindividual variability for the full model are represented in Table 4, with the respective standard errors of the point estimates. This model provides the basis for inferences about covariate effects. In addition, results of the stepwise reduction with respect to goodness of fit are presented in Table 5. In the first reduction step, the removal of intracardiac shunt as a covariate on CL (run 4) resulted in the least change in the MVOF and was removed from the model. In the second reduction step, the removal of bypass time as a covariate on CL (run 6) resulted in the least change in the MVOF and was removed from the model. In the final reduction step, age as a covariate on CL was removed from run 7 (leaving only allometrically scaled weight as a covariate), and the MVOF increased by 41. Finally, when allometrically scaled weight was removed, leaving no covariates (run 8), the MVOF increased by 55. The addition of covariates age, total CPB time, and intracardiac shunt on clearance (run 1, MVOF 5128) resulted in a 58-point reduction in the MVOF when compared with the allometrically scaled weight-normalized model alone (run 7, MVOF 5186) and allowed for inferences about these covariate effects.

Using the final full covariate model, the estimated value of CL is $657 \times (WT/70)^{0.75}$ mL/min for a patient at least 1 month of age with a CPB time of 60 minutes and without right-to-left intracardiac shunt. Observed, versus population and individual predicted, log-transformed concentrations for the full covariate PK model are presented in Figure 2. Observed, population, and individual predicted concentrations versus time for each subject is presented in Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/AA/B180).

Alternate Covariate Model

Scaling the PK parameters linearly to weight resulted in a 4-point reduction in the MVOF when compared with the allometrically scaled model. Final parameter estimates for both the allometric weight-normalized and the

Table 4. Parameter Estimates from the Full Covariate Allometric Weight-Normalized and Weight-Normalized Dexmedetomidine Population PK Models for Typical Subject at Least 1 Month of Age with a Total Bypass Time 60 Minutes and No Right-to-Left Intracardiac Shunt

	Allometric weight-normalized model		Weight-normalized model	
	Point estimate (95% CI from LLP)	SE%	Point estimate (95% CI from LLP)	SE%
θ_{CL} (mL/min)*	657 (600 to 750)	6.24	1170 (1050 to 1300)	5.86
θ_{V1} (L)†	88 (70 to 110)	11.92	88 (70 to 112)	12.05
θ_{Q} (mL/min)‡	6780 (4000 to 20,000)	40.71	12,300 (7000 to 36,000)	40.81
θ_{V2} (L)§	112 (90 to 130)	9.73	112 (95 to 135)	10.27
Age 50% CL (mo)	0.032 (0.015 to 0.055)	34.16	0.014 (0.003 to 0.023)	56.34
TBYP effect CL	−0.31(−0.45 to −0.15)	−23.48	−0.29 (−0.45 to −0.1)	−24.31
Intracardiac shunting CL	1.24 (1.1 to 1.5)	7.49	1.26 (1.1 to 1.5)	7.43
Interindividual variability	CV%	SE%	CV%	SE%
$\omega 2_{CL}$	28.58	18.60	29.51	19.52
$\omega 2_{V1}$	62.21	21.32	61.81	20.37
ω^2_{Q}	157.16	32.96	153.3	34.51
ω^2_{V2}	28.64	39.88	28.14	37.88
Interindividual covariance	Point estimate (correlation)	SE%	Point estimate (correlation)	SE%
Cov CL V1	0.116 (0.65)	30.43	0.133 (0.73)	28.05
Cov CL Q	0.165 (0.37)	54.00	0.178 (0.4)	51.69
Cov V1 Q	0.775 (0.79)	37.16	0.771 (0.81)	34.63
Residual variability	Point estimate	SE%	Point estimate	SE%
$\sigma 2_{proportional}$	19.75	12.67	19.77	12.69
$\sigma 2_{additive}$	3.30	29.91	3.36	30.71

95% confidence intervals derived from LLP for fixed effect parameter estimates are indicated in parentheses. SE% is the standard error percent derived from the NONMEM asymptotic standard errors. Interindividual variability and proportional residual variability point estimates are presented as percent coefficient of variation (square root of variance) × 100. $\sigma 2_{additive}$ point estimate is expressed as a standard deviation.

Allometric weight-normalized model:

*$CL = \theta_{CL} \times (WT/70)^{0.75} \times (Age/(0.032 + Age)) \times (TBYP/60)^{-0.31} \times (1.24$ [right-to-left intracardiac shunt only]).

†$V1 = \theta_{V1} \times (WT/70)$.

‡$Q = \theta_{Q} \times (WT/70)^{0.75}$.

§$V2 = \theta_{V2} \times (WT/70)$.

Weight-normalized model:

*$CL = \theta_{CL} \times (WT/70) \times (Age/(0.014 + Age)) \times (TBYP/60)^{-0.29} \times (1.26$ [right-to-left intracardiac shunt only]).

†$V1 = \theta_{V1} \times (WT/70)$.

‡$Q = \theta_{Q} \times (WT/70)$.

§$V2 = \theta_{V2} \times (WT/70)$.

CI = confidence interval; CL = clearance; COV = covariance; LLP = log-likelihood profiling; Q = intercompartmental clearance; V1 = central volume of distribution; V2 = peripheral volume of distribution.

weight-normalized models are presented in Table 4, with the respective SE% for each point estimate. Results of the stepwise reduction are presented in Table 5.

Model Evaluation

The 95% confidence intervals from log-likelihood profiling for the final model estimates are presented in Table 4. Composites of the log-likelihood profiles are shown in Supplemental Figure 2 (Supplemental Digital Content 2, http://links.lww.com/AA/B181).

Simulations

The concentration-time curves from the simulations are shown in Figure 3. Neonates demonstrate higher plasma concentrations with the same dosing strategy than both 4- and 20-month-old children. The 3 neonates who experience hypotension and required CPR are also represented in Figure 3.

Safety Evaluation

Three infants and 3 neonates had EKG evidence of cardiac ischemia on surveillance EKGs after dexmedetomidine infusion. ST-segment changes were noted in 1 subject each in cohort 1, 3, and 5 and new T-wave inversion in 1 subject each in cohort 1, 4A, and 5 when compared with the EKG performed immediately postoperative. All changes had resolved on surveillance EKGs performed 72 hours after the end of dexmedetomidine infusion. One neonate in cohort 5 had evidence of new ST-segment changes on the surveillance EKG performed 72 hours after discontinuation of dexmedetomidine that was not present on the EKG after the end of infusion. None of these events was considered clinically significant.

One neonate in cohort 5 experienced a transient increase in ALT measurement 3 weeks after discontinuation of dexmedetomidine infusion. No other subjects experienced changes in ALT measurements either immediately after discontinuation of infusion or at follow-up. No subjects experienced ocular dryness or developed symptoms of adrenal insufficiency.

In cohort 3, 1 infant experienced oversedation resulting in responsiveness only to deep stimulation and hypopnea while receiving the dexmedetomidine infusion. The infusion was discontinued with subsequent increase in responsiveness and respiratory effort. No subjects experienced prolonged sedation after discontinuation of dexmedetomidine.

Six subjects developed cardiac arrhythmias while receiving dexmedetomidine. These are summarized in Table 6. Four of these subjects required discontinuation of dexmedetomidine infusion. In addition, 1 infant

Table 5. Results of Stepwise Reduction

Run	Compared with	Description	No. estimated parameters	MVOF	Change in MVOF
Allometric weight-normalized model					
1		Full allometric model	13	5128	
2	1	Age effect on CL removed from full model	12	5144	16
3	1	Bypass time on CL removed from full model	12	5140	12
4	1	Intracardiac shunt effect on CL removed from full model	12	5136	7
5	4	Age effect on CL removed from model 4	11	5163	27
6	4	Bypass time on CL removed from model 4	11	5145	9
7	6	Age effect on CL removed from model 6	10	5186	41
8	7	Allometric weight effect removed from all parameters from model 7 (no covariates)	10	5241	55
Weight-normalized model					
1		Full weight-normalized model	13	5124	
2	1	Age effect on CL removed from full model	12	5129	5
3	1	Bypass time on CL removed from full model	12	5136	12
4	1	Intracardiac shunt effect on CL removed from full model	12	5134	10
5	2	Bypass time on CL removed from model 2	11	5149	20
6	2	Intracardiac shunt effect on CL removed from model 2	11	5147	18
7	6	Bypass time on CL removed from model 6	10	5167	20
8	7	Weight effect removed from all parameters from model 7 (no covariates)	10	5241	74

CL = clearance; MVOF = minimum value of the objective function.

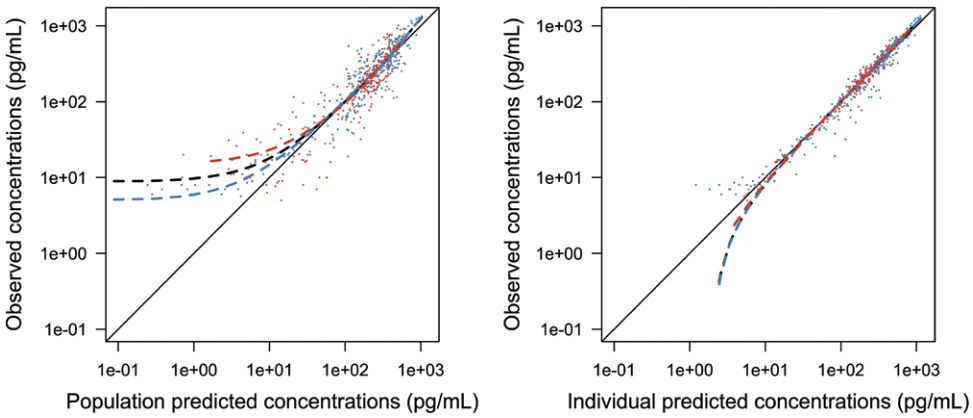

Figure 2. Observed versus population (left) and individual (right) predicted concentrations on log-scale for the full covariate pharmacokinetic model. Infants are represented by blue dots and neonates by orange dots. Lowess smoothers are included for the entire dataset (black dashed line), infant data (blue dashed line), and neonatal data (orange dashed line).

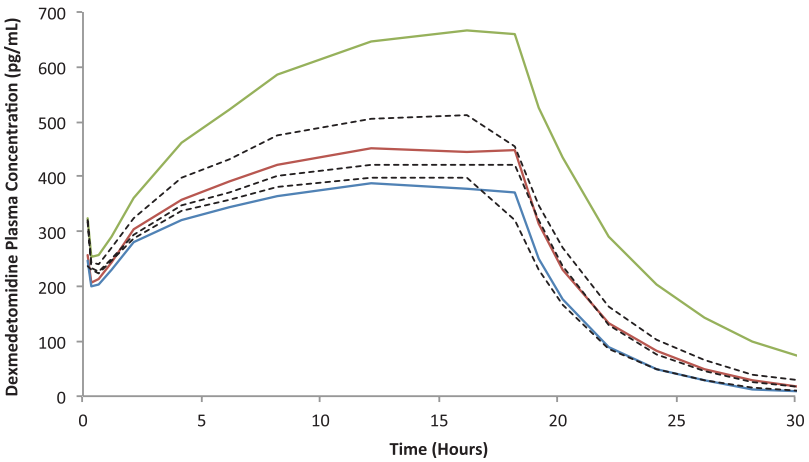

Figure 3. Simulated median plasma concentrations using the full covariate model for the youngest (green line), median (blue line), and oldest child (red line) without intracardiac shunt (0.03 months and 2.8 kg; 4.3 months and 5.8 kg; 20.4 months and 11.9 kg, respectively). A loading dose of 0.5 μg/kg was administered over 10 minutes followed by an infusion of 0.4 μg/kg/h for 18 hours. All 3 subjects were simulated with the median bypass time of 60 minutes. Additional simulations were performed for the 3 neonates who received this dosing regimen yet experienced hypotension requiring CPR (black dashed lines).

in cohort 3 developed hypotension not associated with arrhythmia requiring discontinuation of dexmedetomidine infusion. Three neonates in cohort 5 required CPR while receiving dexmedetomidine. One of these neonates developed atrial ectopy with resultant hypotension and cardiopulmonary insufficiency. Two other

Table 6. Cardiac Arrhythmias During Dexmedetomidine Infusion

Arrhythmia	Dosing cohort	Total subjects	Clinical adverse event	Outcome
Accelerated junctional rhythm	2	1	None	Resolved without intervention
	4	1	None	
Complete heart block	2	1	Bradycardia	Resolved after discontinuation of dexmedetomidine
Junctional rhythm	4A	1	Decreased heart rate	Resolved after discontinuation of dexmedetomidine
Atrial ectopy	5	2	Hypotension	1 subject: Resolved after discontinuation of dexmedetomidine 1 subject: CPR and extracorporeal membrane oxygenation

neonates developed hypotension attributed to cardiac tamponade progressing to cardiopulmonary arrest. After the development of hypotension requiring CPR in these 3 neonates, it was determined that the MTD in neonates was exceeded in cohort 5 (0.4 μg/kg/h). No further neonates were enrolled in cohort 5 or cohort 6. Cohort 4A, loading dose of 0.35 μg/kg and infusion of 0.3 μg/kg/h, was created to further explore the PK profile and safety of dexmedetomidine in neonates. The MTD was neither exceeded nor determined in the infant cohorts.

DISCUSSION

Neonates require an approximately 30% to 40% reduction in weight-based dose (microgram per kilogram) to achieve similar plasma concentrations at steady state when compared with infants, with the greatest reduction required in the first 2 weeks of life. Using an allometrically scaled population PK model, dexmedetomidine demonstrated a plasma drug clearance of $657 \times (WT/70)^{0.75}$ mL/min, intercompartmental clearance of $6780 \times (WT/70)^{0.75}$ mL/min, central volume of distribution of $88 \times (WT/70)$ L, and peripheral volume of distribution of $112 \times (WT/70)$ L for a typical subject >1 month of age with a total CPB time of 60 minutes and without right-to-left intracardiac shunt. Dexmedetomidine pharmacokinetics may be influenced by age during the neonatal period, weight, total bypass time, and intracardiac shunting. After accounting for body size–related changes, CL increases with age until approximately 1 month. The effect of bypass time on CL reveals an inverse relationship. The presence of a right-to-left intracardiac shunt increases CL by 24%. Based on the simulations, time to steady-state concentration (380–450 pg/mL) is approximately 6 hours after the initiation of a loading dose of 0.5 μg/kg followed by a constant-rate infusion of 0.4 μg/kg/h for a typical infant. Neonates achieve higher plasma concentrations (>600 pg/mL) with longer times to steady-state concentration (>10 hours) when administered equivalent microgram per kilogram doses.

The linear scaled model resulted in a relatively poorer precision for the estimates of Q and the age effect on CL, when compared with the allometrically scaled model, despite a relative reduction in MVOF of 4 points for the linear scaled model. The typical estimate of CL at 70 kg in the linear scaled model (1170 mL/min) was nearly twice the value of the typical CL at 70 kg estimated in the allometrically scaled model (657 mL/min). In addition, the estimate of the age effect in the linear scaled model was about half of the value estimated for the allometrically scaled model. The similar goodness of fit for these 2 models does not mask the very different inferences that would be made about model parameters. This apparently paradoxical finding can be resolved when considering other sources of information. When exploring the reliability of the body size–related change in CL, the allometrically scaled model estimate of 657 mL/min at 70 kg is quite consistent with the reported adult value of 650 mL/min for a mean weight of 72 kg (Precedex™, dexmedetomidine product label). This is not surprising, given the large body of evidence supporting allometric scaling for body size–related changes in CL. Given the correlation of age and body size, this also leads to the conclusion that the estimated age-related effects on dexmedetomidine CL are more reliably informed by the allometrically scaled model or that the bias in the body size scaling induced by the linear scaled model may also result in a bias in the age-effect estimate.

A typical full-term newborn at the 50th percentile for weight (3.4 kg) without right-to-left intracardiac shunting, and with a median bypass time of 60 minutes postoperative from cardiac surgery, has a total systemic CL of 10 mL/min/kg (34 mL/min). By the age of 2 weeks, with a corresponding weight of 3.8 kg, CL has more than doubled to 18.2 mL/min/kg (69 mL/min). However, by the age of 1 month at 4.2 kg, CL is 18.4 mL/min/kg (77 mL/min), demonstrating the allometric effect of weight on CL. CL increases dramatically with age, particularly during the first 2 weeks of life. Beyond 1 month, age has minimal effect on CL. CL continues to increase with increasing weight, reaching reported adult values of 650 mL/min.[28–30] The time to steady state is significantly increased in neonates, as demonstrated in the simulations.

Drug metabolism during infancy is dynamic, because the newborn develops rapidly. The exact nature of changes in drug disposition varies by the specific metabolic pathway, because hepatic metabolic enzymes mature at different rates. In a study of 45 children postoperative from cardiac surgery including 4 neonates, Potts et al.[21] studied dexmedetomidine disposition after administration of a single bolus dose. The authors developed a population PK model of dexmedetomidine, including clearance maturation, and found that clearance was reduced at birth (7.9 mL/min/kg) for a 3.4-kg newborn and matured at a half-time of 46.5 weeks, reaching 72% of adult rates by 6 months of age. Although we estimated a very similar clearance of 10 mL/min/kg at birth compared with that in study by Potts et al., the inclusion of 23 neonates and 36 infants in our study allowed us to provide increased insight into the effect of enzyme

maturation on dexmedetomidine clearance in the neonatal period. In contrast to the study by Potts et al., we found that neonatal dexmedetomidine clearance did not mature based on a half-time of 46.5 weeks but instead rapidly increased during the first 2 weeks of life, exhibiting minimal effect on clearance by 1 month of age. More recently, Chrysostomou et al.[31] studied the disposition of dexmedetomidine in initially intubated preterm and term neonates in ICUs and found the median clearance in neonates of 36 to 44 weeks gestational age to be 15 mL/min/kg. They performed a noncompartmental PK analysis and did not apply allometric weight scaling or evaluate the impact of age. Our findings are consistent with the reported maturation of hepatic enzymes responsible for dexmedetomidine metabolism (UGT1A4, UGT2B10, CYP2A6, and *N*-methyltransferase), which mature during the neonatal period.[12,32–35] Limitations to our evaluation of the influence of age include an age gap between 1 and 2.5 months at the completion of enrollment. This is attributed to the patient population studied and the natural timing of surgical correction of various congenital heart defects. However, maturation was found to be essentially complete by the age of 1 month with the evaluation of 23 subjects in this age range.

We previously reported the development of complete heart block and resultant bradycardia in 1 infant in cohort 2 (0.5 μg/kg/h) that resolved after discontinuation of dexmedetomidine, as well as 1 infant in cohort 3 (0.75 μg/kg/h) who developed hypotension requiring discontinuation of infusion.[16] In the neonatal cohorts, 3 subjects developed cardiac bradyarrhythmias requiring discontinuation of infusion. One neonate in cohort 4A (0.3 μg/kg/h) developed junctional rhythm approximately 7 hours after the initiation of the infusion that resolved after discontinuation of dexmedetomidine. One neonate in cohort 5 developed atrial ectopy after the loading dose (0.5 μg/kg over 10 minutes) that also resolved after discontinuation of dexmedetomidine. The remaining neonate from cohort 5 developed atrial ectopy with severe hypotension, requiring CPR and subsequent extracorporeal membranous oxygenation approximately 10 hours after initiation of CIVI (0.4 μg/kg/h). Two other neonates in cohort 5 developed hypotension attributed to cardiac tamponade requiring brief CPR between 2.5 and 5 hours after initiation of CIVI. No PK samples were obtained from these neonates with the exception of the subject from cohort 4A whose dexmedetomidine concentrations were found to be similar to the median concentrations of the other subjects in the same dose cohort. The 3 neonates in cohort 5 who required CPR while receiving dexmedetomidine were between 5 and 8 days old and weighed 2.2 to 3 kg. Simulations showed their plasma concentrations to be within the range of subjects who did not experience hypotension.

A review of the literature reveals conflicting information regarding electrophysiologic changes during dexmedetomidine administration. In a study of 12 children (age, 5 to 17 years), Hammer et al.[36] describe the significant effects on sinus node function with an increase in sinus cycle length (0.788 s compared with baseline 0.606 s) and node recovery time (0.293 vs 0.212 s) when dexmedetomidine was administered as an IV loading dose of 1 μg/kg over 10 minutes followed by CIVI of 0.7 μg/kg/h. Atrioventricular nodal function was also depressed, with prolongation of the PR interval (0.162 vs 0.144 s). In contrast, Chrysostomou et al.[37] studied 51 patients aged 0 to 17 years who were administered dexmedetomidine as a standard of care after open heart surgery and found no significant changes in PR intervals. Although the influence of dexmedetomidine on the bradycardic and hypotensive dose-limiting toxicities experienced in this study cannot be quantified, the degree of severity of those dose-limiting toxicities, specifically in neonatal cohort 5 (0.5 μg/kg to 0.4 μg/kg/h) is out of proportion to the lower dose neonatal cohorts and the infant cohorts. Given the reduced clearance in neonates found in this study, along with the dose-limiting toxicities in the highest neonatal dose cohort studied, dose adjustments should be strongly considered when administering dexmedetomidine to newborns, particularly in the first 2 weeks of life.

In our previous study of the PK of dexmedetomidine in infants after open heart surgery, we initially explored covariates such as CPB time but were limited by a small sample size. Using the combined infant and neonatal dataset, the full covariate model approach in this study allowed for a more detailed evaluation of the effect of covariates on key PK parameters. The point estimate of the bypass time effect associated with a 60-minute bypass indicates a decrease in CL and is deemed statistically significant (based on the 95% confidence interval excluding the null value). The negative values suggest an association between a decrease in CL with longer bypass time.

Subjects with a right-to-left intracardiac shunt demonstrate an increase in clearance of 24%. Patients with single ventricle cardiac anatomy after stage 2 palliation (Glenn or hemi-Fontan procedure) have significant intracardiac shunt with blood flow from the inferior vena cava returning directly to the single ventricle and then to the systemic circulation, thus bypassing the pulmonary circulation. This results in a Qp:Qs of <1 with recirculation of blood through the systemic circulation including the liver. The influence of intracardiac shunt on drug disposition has not been reported in pediatrics. Bokesch et al.[38] studied the effect of right-to-left intracardiac shunt in lambs on lidocaine disposition. Lidocaine is 60% to 80% extracted on first pass through the lungs and has a high hepatic extraction ratio.[39] Lambs with surgically created right-to-left shunts were found to have significantly increased peak whole blood concentrations of lidocaine. This finding may be explained by the shunt-induced reduction in first-pass lung extraction overwhelming any increases in hepatic clearance expected with the increase in systemic blood flow. First-pass lung extraction of dexmedetomidine is unknown, but it is likely to be less important to systemic pharmacokinetics than for lidocaine, as supported by the fact that clearance in our patients with right-to-left shunt was increased, as expected with increased systemic perfusion for a drug with high hepatic extraction.[40]

The population model described here suggests a reduction in dosing of dexmedetomidine in the neonatal period because of a reduced clearance. Weight-based dosing continues to be appropriate with additional dose-adjustment consideration based on age in the immediate newborn period as well as total bypass time and the presence of an intracardiac right-to-left shunt. The MTD in this study

was exceeded at 0.4 μg/kg/h in neonates. The MTD in infants was not determined. In general, continuous infusions up to 0.3 μg/kg/h in neonates and 0.75 μg/kg/h in infants were well tolerated after open heart surgery.

DISCLOSURES

Name: Felice Su, MD.
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Attestation: Felice Su has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
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Attestation: Athena F. Zuppa has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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