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The Population Pharmacokinetics of Dexmedetomidine in Infants After Open Heart Surgery

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Abstract

Background—Dexmedetomidine is a highly selective α_2 -agonist with hypnotic, analgesic and anxiolytic properties. In adults, it provides sedation while preserving respiratory function facilitating extubation. Only limited pharmacokinetic data are available for pediatric patients. The primary aim of this study was to determine the pharmacokinetics of dexmedetomidine in infants after open heart surgery.

Methods—We evaluated 36 infants, ages 1 month-24 months, after open heart surgery. Cohorts of 12 infants requiring mechanical ventilation after open heart surgery were enrolled sequentially to one of three initial loading dose – continuous IV infusion (CIVI) regimens: 0.35–0.25, 0.7–0.5, or 1–0.75 mcg/kg – mcg/kg/hr. The initial loading dose was administered over ten minutes immediately postoperatively followed by a CIVI of up to 24 hours. 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 two-compartment disposition model with weight on drug clearance, intercompartmental clearance,

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Conflict of Interest:

Athena F. Zuppa, MD MSCE (Corresponding Author)

Are there any other potential conflicts or relevant competing interests that should be known by the Editor? Yes ☒ No ☐

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central and peripheral volume of distributions, total bypass time as a covariate on clearance and central volume of distribution, and age and ventricular physiology as covariates on clearance. Infants demonstrated a clearance of 28.1 mL/min/kg^{0.75}, intercompartmental clearance of 93.4 mL/min/kg^{0.75}, central volume of distribution of 1.2 L/kg and peripheral volume of distribution of 1.5 L/kg.

Conclusions—Dexmedetomidine clearance increased with weight, age and single-ventricle physiology, while total bypass time was associated with a trend towards decreasing clearance and central volume of distribution increased as a function of total bypass time. The dependence of clearance on body weight supports current practice of weight-based dexmedetomidine dosing, while the clinical impact of the remaining covariate effects requires further investigation. Initial loading doses in the range of 0.35 to 1 mcg/kg over ten minutes and CIVI of 0.25 to 0.75 mcg/kg/hr were well tolerated in this infant population.

Introduction

Sedation and analgesia are essential in the management of critically ill patients. Opiates and benzodiazepines that are frequently required in this pediatric population often have undesirable side effects, most notably respiratory depression. Dexmedetomidine is a highly selective central α_2 -agonist with anxiolytic, hypnotic and analgesic properties. Its anxiolytic and hypnotic properties result from activation of postsynaptic α_2 -adrenergic receptors located in the locus ceruleus (1,2), while its analgesic properties result from activation of α_2 -adrenergic receptors located in the spinal cord (3,4). Dexmedetomidine is unique in that it provides sedation during the postoperative period while allowing patients to be easily arousable to gentle stimulation. Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine or feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450-mediated metabolism. The major metabolic pathways of dexmedetomidine are: (1) direct N-glucuronidation to inactive metabolites; (2) aliphatic hydroxylation mediated primarily by CYP2A6; and (3) N-methylation of dexmedetomidine.

Pediatric populations who may benefit from the favorable pharmacodynamic effects of dexmedetomidine include neonates, infants and children with congenital heart disease who undergo cardiac surgery. Congenital heart disease is one of the leading causes of death in infants. With an incidence of 8:1000 live births, approximately 20,000 surgical procedures per year are performed to palliate or correct cardiac lesions (5). Tracheal intubation and mechanical ventilation are frequently required in the postoperative period for these patients. Fresh cardiac suture lines mandate that patients remain adequately sedated to decrease the risk of postoperative bleeding. Concurrently, weaning from mechanical ventilation and expedited tracheal extubation can avoid complications of prolonged intubation and facilitate postoperative mobilization and rehabilitation. Dexmedetomidine may provide both adequate sedation during the immediate postoperative period and facilitate timely tracheal extubation after surgery due to its unique pharmacodynamic properties.

Although dexmedetomidine pharmacology has been well studied in adults, limited pediatric pharmacokinetic (PK) and pharmacodynamic data is available to guide therapy, particularly in infants with congenital heart disease. These infants exhibit a wide range of anatomy and physiology, from ventricular septal defects to hypoplastic left heart syndrome. The impact of immature drug-metabolizing enzyme systems, altered physiology, and intraoperative procedures such as cardiopulmonary bypass and hypothermic circulatory arrest on dexmedetomidine drug disposition has not been studied. Understanding the clinical pharmacology of dexmedetomidine is necessary to allow for rational drug administration in this critically ill pediatric subpopulation. The primary objective of this study was therefore

to describe the PK of dexmedetomidine in infants with congenital heart disease postoperatively from open heart surgery.

Methods

Clinical Trial

This study was conducted under an investigational new drug application (IND 69,758) with the Food and Drug Administration. After IRB approval and written informed parental consent, 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 enrolled in a dose escalation trial of an IV initial loading dose followed by a continuous IV infusion (CIVI) of dexmedetomidine:

	<u>Initial Loading Dose</u> (mcg/kg)	<u>Infusion Rate</u> (mcg/kg/hr)
Cohort 1	0.35	0.25
Cohort 2	0.7	0.5
Cohort 3	1	0.75

Doses were chosen to cover the range of doses currently included in the drug monograph. Immediately postoperatively, dexmedetomidine was administered in the cardiac intensive care unit, with the initial dose administered over 10 minutes followed by a CIVI of 4 – 24 hours. Thirty-six evaluable subjects were enrolled with twelve subjects enrolled in each dosing cohort. Interim PK and safety analyses were performed at the completion of each dosing cohort before enrollment at the next higher dose.

Pharmacokinetic Sampling

PK samples, consisting of one milliliter of blood, were drawn immediately before and after the initial dose, after initiation of infusion (0.5, 6, 12 hours), at the end of infusion and after the end of infusion (0.25, 0.5, 1, 2, 4, 8, 12, 24 hours) in the first cohort of subjects. For the second and third cohorts, samples were obtained immediately before the initial dose, after start of infusion (0.5, 1, 2, 4–6 hours), immediately before the end of infusion and after the end of infusion (0.25, 0.5, 1, 2, 4, 8, 12, 15–18 hours). Plasma was separated by centrifugation and stored at -80°C .

Drug Quantitation

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 (6). The intraday and interday coefficients of variation were 0.74 to 6.67% and 0.67 to 4.86% for dexmedetomidine concentrations in the range of 5–1200 pg/mL, respectively.

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). All models were run with the first order conditional estimation with interaction (FOCE-I) 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 the examination of the following criteria: visual inspection of diagnostic scatter plots (observed vs. predicted concentration, observed and predicted concentration vs. time, and weighted residual vs. predicted concentration or time), the precision of the parameter estimates as measured by asymptotic standard errors derived from the covariance matrix of the estimates,

successful minimization with at least 3 significant digits in parameter estimates, changes in the Akaike Information Criterion (minimum value of the objective function plus two times the total number of parameters), and changes in the estimates of interindividual and residual variability for the specified model.

Base Model—One and two-compartment models were investigated. A two-compartment disposition model was deemed optimal to define the dexmedetomidine plasma concentration profile based on results from the model-building process and previously published data (7,8). 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 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 , η_{ki} are the interindividual random effects for individual i and parameter k . Models were explored using various interindividual 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: $C_{obs,ij} = (C_{pred,ij} * (1 + \epsilon_{ijp})) + \epsilon_{ija}$ 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 .

Weight-Normalized Model—Once the base model was selected, a simple weight-normalized model was constructed. The impact of weight was fixed on all PK parameters using a linear normalization: $TVP = \theta_{TVP} * (WT_i / WT_{ref})$ where TVP is the typical value of a model parameter, described as a function of individual body weight, θ_{TVP} is an estimated parameter describing the typical PK parameter value for an individual with weight equal to the reference weight, WT_i is an individual subject's body weight and WT_{ref} is the reference value (7.08 kg for this analysis).

Full Covariate Model—A full covariate model was constructed in order to make inferences about effects of covariates on dexmedetomidine disposition. Covariate effects were predefined based on clinical interest, prior knowledge and physiologic plausibility. 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 data sets (9,10). The full model included effects of age, weight, total cardiopulmonary bypass time and ventricular physiology (one or two-ventricle). The impact of weight on all PK parameters was investigated using an allometric model: $TVP = \theta_{TVP} * (WT_i / WT_{ref})^{\theta_{allometric}}$ which is similar to the linear model, except $\theta_{allometric}$ is an allometric power parameter based on 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 (11). Age was incorporated as a covariate on clearance to account for the maturation of CYP2A6 metabolism. Total bypass time was evaluated as a covariate on clearance, based on the hypothesis that a longer bypass time would impair clearance immediately postoperatively. The effect of total bypass time on central volume of distribution was also of clinical interest and was included in the full model. Finally, ventricular physiology was evaluated as a covariate on clearance to assess the impact of altered blood flow.

For both the weight-normalized and full covariate models, percent median prediction error (MDPE) and median absolute prediction error (MDAPE) were calculated to provide an estimate of model prediction bias and precision, respectively (12). Log-likelihood profiles were also constructed for the full covariate model to evaluate precision of fixed effect parameter estimates.

Simulations—The full covariate model was used to simulate expected concentration-time profiles under various dosing scenarios. Five hundred Monte Carlo simulation replicates of individual patients with typical covariates (weight of 7.08 kg, age of 7.7 months, and 57 minutes of cardiopulmonary bypass) were performed, incorporating interindividual and residual random variability. Dosing scenarios included: no loading dose, a 0.35 mcg/kg loading dose, or a 0.75 mcg/kg loading dose, all followed by a fixed rate infusion of 0.25 mcg/kg/hr. In addition, the impact of cardiopulmonary bypass time on plasma concentrations was evaluated through the same Monte Carlo simulation approach. Five-hundred Monte Carlo simulation replicates were performed for a patient (weight of 7.08 kg, age of 7.7 months) who received an initial loading dose of 0.35 mcg/kg and a fixed rate continuous infusion of 0.25 mcg/kg/hr and either 19, 57 or 169 minutes of cardiopulmonary bypass, to cover the median and range of all evaluable subjects including subject 33. The expected value for the typical individual was obtained by selecting the median plasma concentration-time profile across the simulation replicates. The impact of the loading dose on the time to steady-state concentrations was assessed graphically.

Safety Monitoring

Dose-limiting toxicities included bradycardia, hypotension, oversedation or any serious adverse event possibly, probably or definitely related to dexmedetomidine administration. Bradycardia was defined as heart rate < 60–80 bpm and hypotension was defined as mean arterial blood pressure < 30–50 mmHg (based on age). Oversedation was any sedation resulting in clinically relevant symptoms including difficult arousal with stimulation, bradycardia, hypotension or hypopnea. The maximum tolerated dose was defined as the highest dose at which no more than 2 of 12 subjects experienced a dose-limiting toxicity.

Additionally, serial electrocardiograms (ECGs) 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 > 2mm from pretreatment ECG. Serial alanine aminotransferase (ALT) levels were measured to evaluate for evidence of hepatotoxicity (ALT > 2×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

Study Conduct

Thirty-eight subjects were enrolled in this study to achieve a total of 36 evaluable subjects. Demographics of evaluable subjects are listed in Table 1. The median age and weight of the subjects were 7.8 months and 7.04 kg, respectively. Median (range) duration of infusion was 6.6 (4.2–23.7), 8.6 (2.9–23.8), and 8.7 (4.2–22.7) hours in cohort 1, 2, and 3, respectively, with an overall median duration of infusion of 8.1 hours. Of the two inevaluable subjects, one was withdrawn due to peripheral IV catheter malfunction and the other due to ongoing postoperative hemorrhage with resultant hypotension.

Pharmacokinetic Analysis

Concentration-time profiles are presented in Figure 1. The PK analysis of cohort 1 revealed significant intersubject variability in the post-loading dose concentration (range 123 – 498 pg/mL). These concentrations were included in the final analysis, but the PK sampling strategy was modified and a post-loading dose PK sample was not obtained for dosing cohorts 2 and 3.

Model Building—Initial examination of the data revealed that subject 33 was an outlier with regards to intraoperative and postoperative care. Intraoperatively, subject 33 initially received 95 minutes of cardiopulmonary bypass and 54 minutes of circulatory arrest. After weaning from bypass, the subject was again placed on bypass and received an additional 74 minutes of bypass and 35 minutes of circulatory arrest, for a total of 169 minutes of bypass. The range of bypass times for the remaining 35 subjects was 16 – 99 minutes. Postoperatively, the subject experienced increased pulmonary vascular resistance and delayed tracheal extubation. Therefore, this subject was an outlier with regards to both the total intraoperative support time and postoperative recovery and it was expected that dexmedetomidine disposition in this subject differed from the other 35 subjects.

All models were developed based on data from the 35 subjects. The final model was then applied to all 36 subjects. For both approaches, the final structural model was a two-compartment disposition model with covariance between CL and V1 interindividual random effects. Using FOCE-I estimation, all models minimized with successful execution of the covariance step.

Weight-Normalized Model—Parameters for this model were initially estimated based on data from the remaining 35 subjects (model 1). This model was then applied to all 36 subjects (model 2). Observed versus population and individual predicted values are presented in Figure 2 (model 1). Scaling the PK parameters to weight resulted in an 11-point improvement in the objective function when compared to an unscaled model. Final parameter estimates and interindividual variability for models 1 and 2 are presented in Table 2, with the respective standard errors of the point estimates. Prediction bias, as estimated by %MDPE, was –0.89%, and prediction precision as estimated by %MDAPE was 25.1%.

Full Covariate Model—Model 3 represents the full covariate model applied to the 35 subject subset, and model 4 represents the same model applied to all 36 subjects. Observed versus population and individual predicted values are presented in Figure 3 (model 3). This full covariate model resulted in a 12-point reduction in the objective function when compared to the weight-normalized model. Estimated prediction bias (%MDPE) and precision (%MDAPE) were 2.75%, and 31.2%, respectively.

Final parameter estimates and interindividual variability for models 3 and 4 are presented in Table 3, with the respective standard errors of the point estimates. Log-likelihood profile 95% confidence intervals are also supplied for fixed effects parameters of model 3, and were essentially the same as those calculated from the asymptotic standard errors provided by NONMEM. Using model 3, the estimated typical value of CL is 122 mL/min for a patient who was the median weight of 7.08 kg, median age of 7.7 months, single ventricular physiology, and experienced the median bypass time of 57 minutes ($28.1 \text{ mL/min/kg}^{0.75}$). Calculated estimates of CL and V1 for different weights are presented in Table 4. The impact of age relative to the typical value of CL for a range of ages independent of weight and bypass time is presented in Table 5. The impact of total bypass time relative to the typical value of CL and V1 viewed across total cardiopulmonary bypass times is presented

in Table 6. The relative effect of differences in ventricular physiology is presented in Table 3.

There was no systematic bias in the estimation of plasma concentrations for the entire study. This is presented in Figures 4 and 5, which illustrate the log (predicted/population predicted) concentrations and log (predicted/individual predicted) concentrations for models 1 (weight-normalized model) and 3 (full covariate model), respectively. This is also presented in Figure 6, which shows a plot of the observed, population-predicted, and individual-predicted concentrations versus time for the full covariate model.

Simulations—Simulated median concentrations achieved without an initial loading dose, or with a loading dose of 0.35 or 0.75 mcg/kg, followed by an infusion of 0.25 mcg/kg/hr, are shown in Figure 7. A loading dose to infusion ratio of 1.4:1 did not appear to significantly shorten the time to steady-state, whereas a ratio of 3:1 (0.75 mcg/kg:0.25 mcg/kg/hr) resulted in rapidly achieving steady-state concentrations. The simulated concentration-time profiles were similar for the various bypass times. We hypothesize that this is a result of the effects of bypass time on clearance and central volume of distribution; a longer bypass time will result in a lower clearance (higher plasma concentrations) and a larger central volume of distribution (lower plasma concentrations).

Safety Evaluation

One subject each in the first and third cohorts had increasing ST segment elevation and one other subject in the first cohort had new T-wave inversion on the ECG obtained after discontinuation of dexmedetomidine infusion when compared with the ECG immediately postoperatively which resolved within 72 hours after the end of infusion. No subjects had elevations in their ALTs after dexmedetomidine infusion or at long-term follow-up. No subjects experienced ocular dryness or developed symptoms of adrenal insufficiency.

Two cardiac adverse events possibly related to dexmedetomidine infusion occurred in the second cohort. One subject, after a Rastelli procedure, developed intermittent accelerated junctional rhythm that was not clinically significant. A second subject developed intermittent complete heart block after a bidirectional Glenn and atrial septectomy resulting in bradycardia and discontinuation of dexmedetomidine infusion. No clinically significant hypotension occurred in any of the 36 evaluable subjects.

In the third cohort, one subject experienced oversedation resulting in responsiveness only to deep stimulation and hypopnea while receiving the dexmedetomidine infusion. The infusion was discontinued with a subsequent increase in responsiveness and respiratory effort. The maximum tolerated dose was not exceeded nor determined.

Discussion

A typical infant (two-ventricle physiology, median weight of 7.08 kg, median age of 7.7 months, and median bypass time of 57 minutes) after cardiac surgery had a total systemic CL of 28.1 mL/min/kg^{0.75}, Q of 93.4 mL/min/kg^{0.75}, V1 of 1.2 L/kg and V2 of 1.5 L/kg. CL and V1 increased with increasing weight. The effect of bypass time on CL and V1 revealed a trend towards an inverse relationship between bypass time and CL, and a direct relationship between bypass time and V1, but both estimates were relatively imprecise. An effect on increasing CL with increasing age remained after accounting for weight, although this effect was poorly estimated. Subjects with single versus two-ventricle physiology were associated with an increase in clearance (95% confidence interval) of 22% (1% – 49%). Time to steady-state concentration was approximately 6 hours after the initiation of a constant-rate infusion for a typical infant. A ratio of IV initial loading dose administered

over ten minutes: continuous infusion of 3:1 appears to achieve steady-state concentrations rapidly after administration.

Dexmedetomidine is increasingly used postoperatively for children with congenital heart disease. Chrysostomou et al describe their experience in 38 pediatric patients after surgery (13). However, published PK data in the pediatric population are limited. Petroz et al describe 36 children (mean weight 20 kg) who received dexmedetomidine over a ten minute interval (7). They reported a CL of 13 mL/min/kg, using a two-compartment model. This is consistent with the current model-based estimate of 13.3 mL/min/kg for a 20 kg child (Table 4). Diaz et al describes 10 children (median weight 11.5 kg) who received postoperative infusions also using a two-compartment model (8). They report a CL of 0.57 L/hr/kg (9.5 mL/min/kg). The full covariate model presented herein predicts a CL of 15.3 mL/min/kg for an 11.5 kg child. The discrepancy in CL estimation between the two studies is unclear. However, weight was not used as covariate in the determination of CL in the Diaz et al analysis, contrary to the Petroz et al study. Reported CL estimates in adults (805 mL/min, 751 mL/min)(14,15) were also consistent with the full covariate model-based, allometrically extrapolated value of 681 mL/min for a 70 kg adult (Table 4). This finding contributes to the growing empirical evidence in support of allometrically based body size scaling of PK parameters, an observation which is well established and based on a theoretical derivation (11,16). It is because of the allometric nature of physiologic processes, such as systemic clearance, that linearly weight-normalized (mL/min/kg) CL estimates appear to result in greater clearance in smaller children; note the 2-fold change in CL/kg when moving from an adult weight of 70 kg to a 5 kg infant (Table 4). In actuality, the body size effect on CL is consistent across the entire weight range when adjusted by an appropriate size metric (e.g. $\text{weight}^{0.75}$).

For the population studied, there was not a large difference in predictive performance between the weight-normalized model and the full covariate model. While the full covariate model should be used for inferences about covariate effects, the weight-normalized model is the most parsimonious model for purposes of prediction of dexmedetomidine concentrations. Both are consistent with weight-based dosing in this age group. This study was designed to describe dexmedetomidine disposition in infants after cardiac surgery. The sample size and design were optimized to achieve typical PK end points and was successful in this respect, as evidenced by the good precision of typical values of PK parameters. This study was not powered to account for additional confounders such as blood loss and volume repletion. Similarly, the small sample size limits the ability to adequately correct for outliers such as subject 33. The inclusion of subject 33 into the final model resulted in an increase in the absolute values of the bypass effect on both CL and V1. We hypothesize that this was due to this subject's long bypass time. In addition, the broad 95% confidence intervals for the estimated effects of bypass time and age on CL and V1 indicated that these parameters were poorly estimated, and could only be deemed as hypothesis-generating findings. This is again demonstrated in the 95th percentile confidence intervals generated by the log-likelihood profiles. The point estimates of the age effect ranged from -19% to +12% of the typical value as age increased in this study population, potentially reflecting development of CYP2A6 oxidative metabolism capacity, although estimation precision of this effect indicated a relative lack of information about age-dependence in the current data set. The point estimate of the bypass time effect indicated a trend toward decreased CL, with an estimated decrease of up to 10% at a bypass time of 140 minutes. However, an increase in bypass was associated with an increase in V1 of up to 63% at 140 minutes. It is also hypothesized that, if clinically relevant, this bypass-related decrement in CL and increase in V1 may be transient, but further investigation is needed. Single versus two-ventricle physiology was associated with a 22% increase in clearance (95% confidence interval = 1%

- 49%). Again, further investigation with a larger sample size is warranted to describe the clinical relevance of ventricular physiology on dexmedetomidine CL.

Of the 38 subjects enrolled in this study, three subjects experienced cardiac ischemia and one subject experienced intermittent accelerated junctional rhythm; none were considered clinically significant. The relationship of these events with respect to dexmedetomidine is difficult to ascertain given these events occurred in the immediate postoperative period after cardiac surgery. These events do not appear to be dose related as they occurred across all dosing cohorts. One subject in cohort 2, after bidirectional Glenn and atrial septectomy, experienced clinically significant bradycardia due to intermittent complete heart block. The arrhythmia did not recur after discontinuation of infusion and was categorized as a dose-limiting toxicity possibly related to drug. One subject in the third cohort experienced deep sedation requiring discontinuation of infusion. This subject's plasma concentrations were found to be similar to the median concentrations of this dosing cohort.

The population model described here may result in a more rational pharmacologic dosing of dexmedetomidine in this pediatric subpopulation and can provide a basis to explore the relationship between drug exposures and drug effect. Weight-based dosing in this population is reasonable, based on the impact of weight on V1 and CL. The requirement for additional dose-adjustment based on age, total bypass time, and ventricular physiology will require further investigation. Initial loading doses in the range of 0.35 to 1 mcg/kg over ten minutes and CIVI of 0.25 to 0.75 mcg/kg/hr were well tolerated in this critically ill infant population with few adverse events. Given the nonlinear dependence of CL on body weight already described, it is conceivable that higher infusion rates per kg may be beneficial in younger infants. Unfortunately, the therapeutic window for this critically ill pediatric population remains poorly defined and the maximum tolerated dose in this population may be higher than the doses currently included in the drug monograph. The generalizability of this guidance across the age and developmental continuum will be further evaluated after the completion of ongoing and planned trials across a broader range of ages.

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Figure 1.

Concentration-time plots for dexmedetomidine for the three dosing cohorts. Linear plots are represented on the left, with semilogarithmic plots represented on the right. Pre-bolus concentrations are omitted from semilogarithmic plot. Plasma concentrations obtained before and after end of infusion (EOI) are shown. EOI occurs at 0 hours. “A” panels represent dosing cohort 1: IV loading dose administered over ten minutes of 0.35 mcg/kg followed by a continuous IV infusion (CIVI) of 0.25 mcg/kg/hr; “B” panels represent dosing cohort 2: loading dose of 0.7 mcg/kg followed by a CIVI of 0.5 mcg/kg/hr; “C” panels represent dosing cohort 3: loading dose of 1 mcg/kg followed by a CIVI of 0.75 mcg/kg/hr.

Figure 2. Observed versus population (left) and individual (right) predicted concentrations for the weight effect only dexmedetomidine pharmacokinetic model derived without subject 33 (model 1). Data are plotted using individual subject identification numbers. A loess smoother is represented by the dashed line.

Figure 3.

Observed versus population (left) and individual (right) predicted concentrations for the full model pharmacokinetic model derived without subject 33 (model 3). Data are plotted using individual subject identification numbers. A loess smoother is represented by the dashed line.

Figure 4. Log (measured concentrations/population predicted concentrations) vs. time and log (measured concentrations/individual predicted concentrations) vs. time for model 1 (weight-normalized model)

Figure 5.

Log (measured concentrations/population predicted concentrations) vs. time (left) and log (measured concentrations/individual predicted concentrations) vs. time (right) for model 3 (full covariate model)

Figure 6. Observed (solid circles), population (dashed line) and individual predicted (solid line) dexmedetomidine concentrations versus time for all 36 subjects using model 4.

Figure 7.

Simulated expected plasma dexmedetomidine concentrations for a patient (weight of 7.08 kg, age of 7.7 months, 2-ventricle physiology and 57 minutes of cardiopulmonary bypass) who received a continuous infusion of 0.25 mcg/kg/hr without a loading dose (bottom line), an IV loading dose of 0.35 mcg/kg administered over ten minutes followed by a continuous infusion of 0.25 mcg/kg/hr (middle line) or an IV loading dose of 0.75 mcg/kg administered over ten minutes followed by a continuous infusion of 0.25 mcg/kg/hr (top line) using model 3.

Table 1

Subject demographics

	Dosing Cohort 1	Dosing Cohort 2	Dosing Cohort 3	Overall
Age (months), median (range)	9.3 (3.3-20.4)	7.8(3.9-18.5)	7.2(2.6-19.6)	7.8
Weight (kg), median (range)	7.5(5.3-11.9)	7.0(5.4-10.2)	6.9(5.1-11.2)	7.0
Gender				
Female	5	6	5	16
Male	7	6	7	20
Surgical procedure				
Two-ventricle physiology				17
Atrial septal defect repair			1	
Common atrioventricular canal repair		1		
Right ventricle - pulmonary artery conduit revision	1			
Subaortic membrane resection		1		
Partial anomalous pulmonary venous return repair	1			
Rastelli		1	1	
Ross-Kono		1		
Tetralogy of Fallot repair	3	1	2	
Ventricular septal defect repair	2		1	
Single-ventricle physiology				19
Bidirectional Glenn	5	4	3	
Bidirectional Glenn & Damus-Kaye-Stansel		1		
Bidirectional Glenn & TAPVR * repair			1	
Kawashima			1	
Hemi-Fontan		2	2	
Cardiopulmonary bypass (minutes), median (range)				
Total bypass	52.5 (16-70), n=12	60 (24-99), n=12	58 (28-169), n=12	59
Cross-clamp	19 (8-53), n=9	29 (13-61), n=10	26 (17-90), n= 11	26
Circulatory arrest	28,n=1	15(2-31),n=5	25 (17-89), n=7	25

* TAPVR - Total anomalous pulmonary venous return

Table 2

Parameter estimates from the weight-normalized dexmedetomidine population pharmacokinetic models without (1) and with subject 33 (2)

Model 1			Model 2	
Parameter	Estimate	SE%	Estimate	SE%
CL (mL/min)	136	5.5	134	5.5
V1 (L)	7.6	20.3	7.6	18.9
Q (mL/min)	412	15.7	426	15.5
V2 (L)	10.5	8.8	10.5	8.8
Parameter	Interindividual Variability	SE%	Interindividual Variability	SE%
ω^2_{CL}	30.3	29.3	31.4	27.1
ω^2_{V1}	68.7	32.4	67.11	32
Residual Variability	Variance	SE%	Variance	SE%
$\sigma^2_{proportional}$	0.04	17.4	0.04	16.5
$\sigma^2_{additive}$	32.3	37.2	16.5	37.6

SE% = (standard error/parameter estimate) *100

Interindividual variability = (square-root of variance) *100

Covariance between CL and V1 random effects was 0.1 (50.4% SE) for model 1 and 0.1 (50.7% SE) for model 2

Final model developed without subject 33:

$CL = \theta_{CL} * (WT / 7.08)$

$V1 = \theta_{V1} * (WT / 7.08)$

$Q = \theta_Q * (WT / 7.08)$

$V2 = \theta_{V2} * (WT / 7.08)$

Table 3

Parameter estimates from the full covariate dexmedetomidine population pharmacokinetic models without (3) and with subject 33 (4). 95th percentile confidence intervals for fixed effect parameter estimates for model 3 are indicated in parentheses and were derived from log-likelihood profiling.

Model 3			Model 4	
Parameter	Estimate	SE%	Estimate	SE%
CL (mL/min)	122 (105, 141)	8.0	119	7.4
V1 (L)	8.5 (6, 11.5)	15.3	8.3	15.3
Q (mL/min)	405 (260, 550)	13.9	419	13.9
V2 (L)	10.3 (8.4, 12)	7.8	10.3	7.8
Age effect CL	0.10 (−0.07, 0.28)	88.0	0.10	89.9
TBYP effect CL	−0.12 (−0.35, 0.11)	98.3	−0.18	53.8
TBYP effect V1	0.54 (0, 1.1)	55.6	0.44	58.9
Single-Ventricle effect CL	1.22 (1.01, 1.49)	10.2	1.24	9.8
Parameter	Interindividual Variability	SE%	Interindividual Variability	SE%
ω^2_{CL}	26.8	25.2	26.8	24.1
ω^2_{V1}	61.9	27.67	61.5	26.5
Residual Variability	Variance	SE%	Variance	SE%
$\sigma^2_{proportional}$	0.04	17.3	0.04	16.3
$\sigma^2_{additive}$	34.3	35.6	34.0	35.0

Covariance between CL and V1 random effects was 0.08 (47.2% SE) for model 3 and 0.08 (44.6% SE) for model 4

Full covariate model developed without subject 33:

$$CL = \theta_{CL} * (WT / 7.08)^{0.75} * (AGE / 7.7)^{0.1} * (TBYP / 57)^{-0.12} * [1.22(\text{for single-ventricle only})]$$

$$V1 = \theta_{V1} * (WT / 7.08)^1 * (TBYP / 57)^{0.54}$$

$$Q = \theta_Q * (WT / 7.08)^{0.75}$$

$$V2 = \theta_{V2} * (WT / 7.08)^1$$

Table 4

Clearance and central volume of distribution calculated values for various weights, estimated using the full covariate model with a median age of 7.7 months and a median total bypass time of 57 minutes

Wt (kg)	Clearance		V1	
	mL/min	mL/min/kg	L	L/kg
5	94.1	18.8	6.0	1.2
7	121.1	17.3	8.4	1.2
12	181.4	15.1	14.4	1.2
20	266.1	13.3	24.0	1.2
70	680.9	9.7	84.1	1.2

Table 5

Percent effect of age relative to typical value of clearance (age = 7.7 months) for various ages. Confidence intervals were derived from log-likelihood profiling.

Age (months)	Percent Effect on Typical CL (95% CI Using Asymptotic Standard Errors)	Percent Effect on Typical CL (95% CI Using Log Likelihood Profiles)
1	81 (57, 116)	81 (56, 115)
6	98 (93, 102)	98 (93, 102)
12	105 (97, 113)	105 (97, 113)
18	109 (94, 126)	109 (94, 127)
24	112 (92, 137)	112 (92, 137)

Table 6

Percent effect of total bypass time relative to the typical value of clearance and central volume of distribution (total bypass time = 57 minutes) viewed across various total bypass times. Confidence intervals were derived from log-likelihood profiling.

Total Cardiopulmonary Bypass Time (min)	Percent Effect on Typical (95% CI)	Percent Effect on Typical V1 (95% CI)
15	117 (86, 160)	48 (23, 100)
40	104 (96, 113)	82 (68, 100)
65	98 (96, 101)	107 (100, 116)
90	95 (85, 105)	128 (100, 165)
115	92 (78, 108)	147 (100, 216)
140	90 (73, 110)	163 (100, 269)