Title:	**Dose Escalation Pharmacokinetic Study of Intranasal Atomized Dexmedetomidine in Pediatric Patients with Congenital Heart Disease**
Short Title	Pediatric Pharmacokinetics of Intranasal Dexmedetomidine
Drug or Device Name(s):	Dexmedetomidine
FDA IND	
Regulatory Sponsor:	Dr. Athena Zuppa
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Amendment 1 Date:	Amendment 3 Date:
Amendment 2 Date:	Amendment 4 Date:

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Events
ALT	Alanine Aminotransferase
ASA	American Society of Anesthesiology
BPM	Beats per minute
CHOP	Children's Hospital of Philadelphia
CICU	Cardiac Intensive Care Unit
CPRU	Cardiac Prep and Recovery Unit
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicities
FDA	Federal Drug Administration
HR	Heart Rate
ICU	Intensive Care Unit
IDS	Investigational Drug Services
IN	Intranasal
IV	Intravenous
MAP	Mean Arterial Pressure
mL	Milliliter
MTD	Maximum tolerated dose
NIH	National Institutes of Health
ORC	Office of Research Compliance
PACU	Post Anesthesia Care Unit
PD	Pharmacodynamics
PG	Picograms
PK	Pharmacokinetics
SAE	Significant adverse events
SBP	Systolic Blood Pressure
UMSS	University of Michigan Sedation Scale

ABSTRACT

Context:

The main goals of premedication in children are to facilitate a smooth separation from the parents and to ease the induction of anesthesia. Dexmedetomidine is a highly selective a_2-adrenergic receptor agonist with sedative, anxiolytic, and analgesic properties. While off-label in its use, intranasal dexmedetomidine is becoming a popular premedication and sedative in children because it is easily administered and well tolerated. Although it appears that intranasal dexmedetomidine is a safe, effective premedication in children, little data have been published regarding its onset time, duration of action, and optimal dose.

Objectives:

Primary

- To determine peak plasma drug concentration level of dexmedetomidine following intranasal administration.
- To determine time of peak drug concentration level of dexmedetomidine following intranasal administration.
- To perform inter-subject cohort dose escalation of intranasal dexmedetomidine guided by associated dose-limiting adverse events and/or maximum plasma level not to exceed 1000 pg/mL.

Secondary

- To determine if dexmedetomidine pharmacokinetics are age dependent.
- To determine if dexmedetomidine pharmacokinetics are different when administered intranasally to patients who are spontaneously ventilating versus those that are mechanically ventilated via an oral endotracheal tube.

Study Design:

Prospective open-label inter-subject cohort dose-escalation pharmacokinetic and pharmacodynamic study

Setting/Participants:

Children's Hospital of Philadelphia

Single Center

Pediatric cardiac catheterization laboratory

Children age ≥1 mo to ≤ 6 yr undergoing an elective diagnostic or interventional cardiac catheterization procedure estimated to last greater than 2 or 3 hours depending on the cohort

Study Interventions and Measures:

Intranasal dexmedetomidine

Dexmedetomidine plasma concentration will be determined using a validated high-performance liquid chromatography-tandem mass spectrometry assay at times: 0, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 minutes post drug administration.

PROTOCOL SYNOPSIS

Study Title	**Dose Escalation Pharmacokinetic Study of Atomized Intranasal Dexmedetomidine in Pediatric Patients with Congenital Heart Disease**
Funder	J.J Templeton Endowed Chair Funds
Clinical Phase	Phase I
Study Rationale	The high anxiety levels that children may experience during the preoperative period may be associated with negative medical, psychological, and social consequences. To reduce this stress, and to facilitate separation from parents and the induction of anesthesia, children are often given a sedative prior to undergoing a procedure. Dexmedetomidine is a highly selective a_2-adrenergic receptor agonist with sedative, anxiolytic, and analgesic properties. While off-label in its use, the administration of dexmedetomidine by the intranasal route has become a popular and effective technique for sedation in children because it is non-invasive, easy to administer, well tolerated, and relatively fast in onset. Despite this, little consistent data have been published on its onset time, duration of action, or optimal dose. The only available PK data on dexmedetomidine in pediatric patients is in children who were administered IV dexmedetomidine. We are proposing a prospective open-label inter-subject cohort dose-escalation pharmacokinetic study to obtain peak dexmedetomidine drug concentration level in plasma and the corresponding time point following intranasal administration in the pediatric patient with cardiac disease.
Study Objective(s)	**Primary** • To obtain peak drug concentration level of dexmedetomidine following intranasal administration. • To determine time of peak drug concentration level of dexmedetomidine following intranasal administration. • To perform inter-subject cohort dose escalation of intranasal dexmedetomidine guided by associated dose-limiting adverse events and maximum plasma concentration. **Secondary** • To determine if dexmedetomidine pharmacokinetics are age dependent. • To determine if dexmedetomidine pharmacokinetics are different in patients who are spontaneously ventilating with a natural airway versus those that are mechanically ventilated via an oral endotracheal tube at the time of intranasal drug administration.

Test Article(s) *(If Applicable)*	Study Interventions: Intranasal dexmedetomidine 2 μg/kg Intranasal dexmedetomidine 4 μg/kg Interim PK and safety analysis will be performed at the completion of each dosing cohort before enrollment in the next higher dose. Subsequent doses will be determined by the defined maximum tolerated dose (MTD).
Study Design	Prospective open-label inter-subject cohort dose-escalation pharmacokinetic study
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Male or female subjects age ≥1 mo to ≤6 yo. 2. Subjects must have congenital heart disease. 3. ASA Physical Status 1-3. 4. Subjects mechanically ventilated via an oral endotracheal tube scheduled for elective cardiac interventional or diagnostic catheterization anticipated to last ≥ 3hours. 5. Subjects spontaneously ventilating with a natural airway scheduled for elective cardiac interventional or diagnostic catheterization anticipated to last ≥ 2hours. 6. Subjects must have reliable intravascular access from which to draw blood samples. **Exclusion Criteria** 1. History of allergic reaction or sensitivity to dexmedetomidine. 2. Nasal pathology preventing the administration of drug. 3. Patients that are on maintenance medications that could inhibit or induce the CYP2A6 enzyme (See Appendix I for full list of CYP2A6 inhibitors and inducers.) 4. Cardiac conduction abnormalities defined as second or third degree heart block or pacemaker dependence. ***5.*** Bradycardia, defined by age, upon arrival in the preoperative care area. 6. Hepatic dysfunction defined as a history of hepatic dysfunction AND an ALT value greater than 2 times normal in the 6 months prior to study drug administration. 7. The subject has received dexmedetomidine or clonidine within 1 week of the study date. 8. BMI >30.

	9. Patients previously enrolled in this study. 10. Any investigational drug use within 30 days prior to enrollment. 11. Wards will not be eligible.
Number of Subjects	It is expected that approximately 65 subjects will be enrolled to produce 42 evaluable subjects. Additional subjects may be required: • If there is a statistically significant difference (>30%) between patients who are under general anesthesia versus those under sedation with a natural airway. • For additional dosing cohorts based on defined MTD.
Study Duration	Each subject's participation will last for up to 6 hours from the time of drug administration. The entire study is expected to last for 15 months.
Study Phases **Screening** **Study Treatment** **Follow-Up**	**Screening** • Subjects who satisfy the screening evaluation and selection criteria as outlined in Section 3.1.1 may be enrolled the study. **Study Treatment** • Preoperative management o The preoperative evaluation and care will be performed in accordance with CHOP CPRU protocol. o The study investigator will confirm that the subject's preoperative vital signs are within the age appropriate normal range. o A rhythm strip will be performed and reviewed by the study team for any exclusion criteria. • Intraoperative management: o Following induction of anesthesia/ sedation, intravascular access necessary for the heart catheterization will be placed by the interventional cardiologist. This access will be used for serum sampling. o The study drug will be obtained from the IDS pharmacy and will be administered via atomizer (Teleflex® LMA® MAD Nasal™ Intranasal Mucosal Atomization Device, MAD300) (See Attachment) intranasally by 1 of 2 physician members of the study team. o Serum dexmedetomidine levels will be drawn at approximately 0, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 minutes post drug administration.

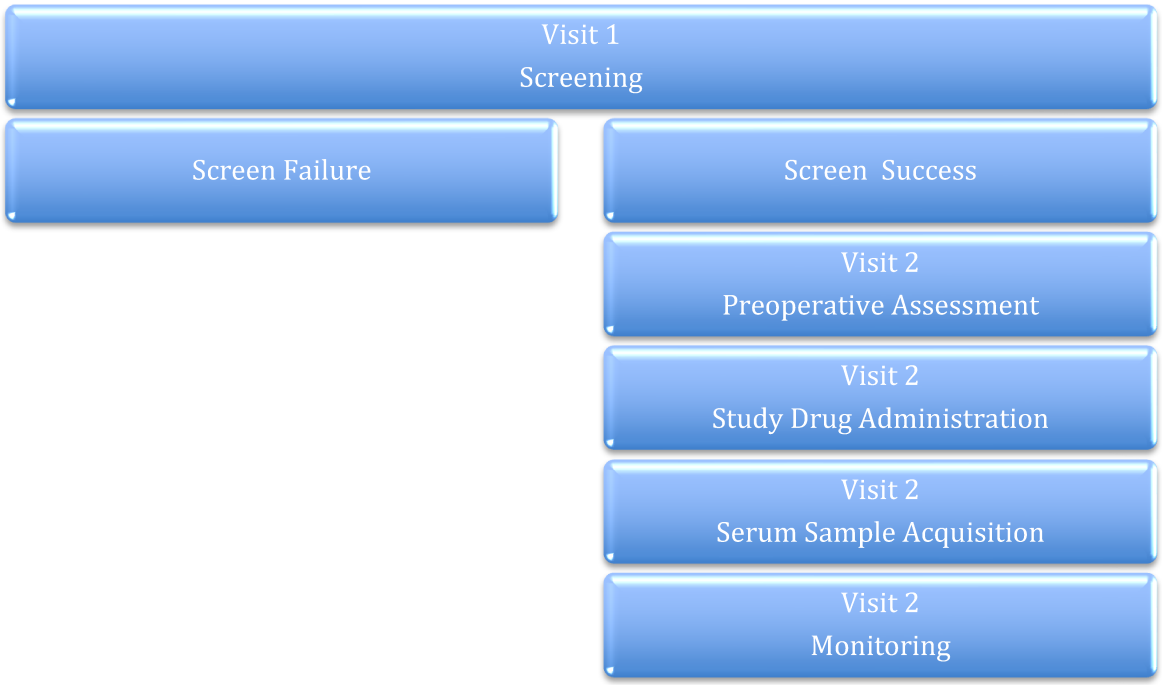
	○ Intraoperative heart rate, rhythm, blood pressure and pulse oximetry will be monitored continuously by the anesthesia team for the duration of the heart catheterization. ○ At the completion of the procedure, the patient will be transported to the PACU or ICU for recovery. The patient will undergo normal postoperative monitoring and care per standard CHOP CPRU or CICU management. ○ The total duration of monitoring will be for approximately 6 hours from the time of study drug administration. ○ If the invasive monitoring lines are removed prior to the completion of the sampling period, no additional samples will be collected unless the patient has vascular access that permits blood draws OR a scheduled phlebotomy is performed for clinical indications AND the subject has not received IV dexmedetomidine as part of their normal anesthesia care. Follow-Up ○ The subject will be continuously monitored for approximately 6 hours from the time of drug administration. There is no additional follow-up.
Efficacy Evaluations	None
Pharmacokinetic Evaluations	Dexmedetomidine plasma concentration will be determined using a validated high-performance liquid chromatography-tandem mass spectrometry assay. Samples will be drawn at approximately 0, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 minutes post drug administration.
Safety Evaluations	Heart rate, rhythm, pulse oximetry, blood pressure and ECG monitoring will be performed throughout the study period. Dose-limiting toxicities (DLT) include bradycardia, hypotension, new intraventricular conduction delay, or any serious adverse event possibly, probably, or definitely related to dexmedetomidine administration. The maximum tolerated dose (MTD) is defined as the highest dose at which no more than 1 of 7 subjects in a cohort experiences a dose-limiting toxicity OR no more than 1 of 7 subjects in a cohort has a blood level in excess of 1000 pg/mL.
Statistical And Analytic Plan	Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations

	for continuous variables such as age and percentages for categorical variables such as gender). Description of pharmacokinetic parameters to be assessed and methods to be employed to calculate those parameters are further discussed in section 6.3. Plasma concentration will be assessed for correlation with anesthetic method at the time of drug administration (ie, sedation in the spontaneously ventilating patient versus general oral endotracheal intubation) in the first dosing cohort. If a greater than 30% difference in plasma concentration is seen between these 2 populations, subsequent dosing cohorts will expand to include patients who are both spontaneously ventilating versus those receiving general oral endotracheal intubation after IRB and FDA approval.
DATA AND SAFETY MONITORING PLAN	Data will be abstracted from the electronic medical record and entered into the database. Data quality will be assessed by regular review of completed Case Report Forms (CRFs) by the Principal Investigator throughout the course of the study. Interim PK and safety analysis will be performed at the completion of each dosing cohort before enrollment in the next higher dose. An independent Medical Monitor who is an anesthesiologist that is not an investigator on the study will be responsible for assessing and monitoring study safety.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Open-Label Treatment**	
Visit Number		**1: Day of Surgery Preoperative Period**	**1: Day of Surgery Intraoperative Period**
Study Days	**-14 to -1**	**0**	**0**
Informed Consent/Assent	X		
Review Inclusion/Exclusion Criteria	X	X	
Demographics/Medical History	X		
EKG Rhythm Strip		X	
Prior/Concomitant Medications	X	X	
Dispense Study Drug			X
Drug Compliance			X
Drug Administration			X
Serum Sample Acquisition			X
Adverse Event Assessment			X

FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

One of the challenges for pediatric anesthesiologists is to minimize distress for children undergoing procedures requiring anesthesia by facilitating separation from their parents and enabling a smooth induction of anesthesia. These difficulties are especially prevalent in patients who require multiple repeat procedures. Midazolam, a γ-amino-butyric acid (GABA) receptor inhibitor, is the most commonly used sedative drug for premedication in children. It has been demonstrated that midazolam administered orally at 0.5 mg/kg is efficacious in producing sedation, reducing anxiety and improving the conditions for induction of anesthesia. However the acceptability of oral midazolam by pediatric patients is only 70% and it has been associated with adverse effects such as agitation, paradoxical hyperactive reaction, and negative postoperative behavioral changes.

Dexmedetomidine is a highly selective a_2-adrenergic receptor agonist with sedative, anxiolytic, and analgesic properties. Since 1999, it has been approved by the FDA for use in adult patients as a short-term (<24 hour) sedative and analgesic in intensive care units and for procedural sedation of non-intubated adult patients. While off-label in its use, the administration of intranasal dexmedetomidine has become a popular technique for sedation in children because it is non-invasive, well tolerated, easily administered, and relatively fast in onset. Although it is established that intranasal dexmedetomidine is an effective sedative for premedication in children, little data have been published on its onset time, duration of action, or optimal dosing. In healthy adult males, peak plasma concentrations of intranasally administered dexmedetomidine were reached in 38 (15-60) minutes and its absolute bioavailability was 65% (35-93%)(median and ranges)(1-2). Yuen et al (3), in a randomized, crossover evaluation of healthy adult volunteers, demonstrated that intranasal dexmedetomidine 1 and 1.5 μg/kg produced sedation in 45-60 min and peaked in 90-105 min. In the pediatric population, studies (4-7) have reported the time to adequate sedation anywhere from 5 to 60 minutes. Variations in these studies include patient age, dosage, route of administration (atomizer vs dropper), indication, clinical endpoint, and sedation scoring scales.

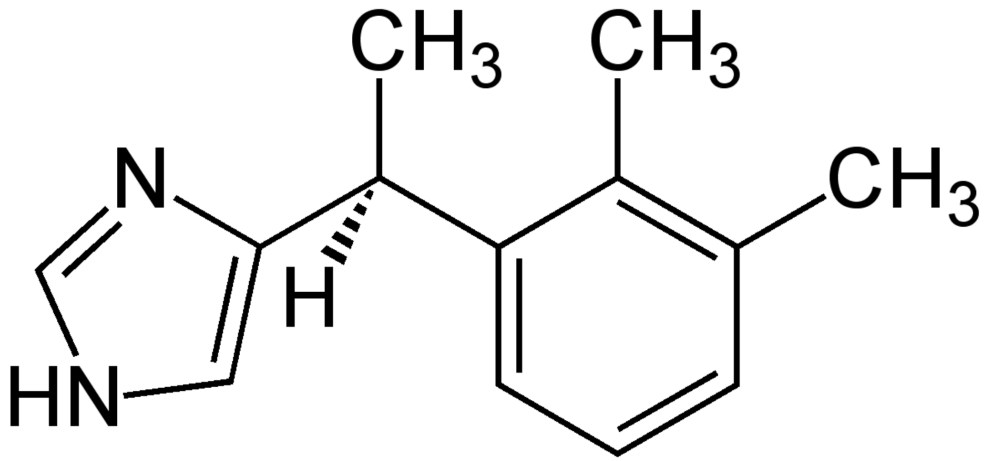
The optimal dose of intranasal dexmedetomidine for pre-operative sedation is unknown. Clinical trials have demonstrated that intranasal dexmedetomidine in a dose of 1 μg/kg produces satisfactory sedation in between 53% and 77% of children at anesthetic induction (6-8). When intranasal dexmedetomidine was administered in doses of 1 μg/kg and 2 μg/kg for premedication in children aged 1-8 years approximately 53% and 66% of children, respectively, were satisfactorily sedated at the time of anesthetic induction (9). When intranasal dexmedetomidine was used as a primary sedative for transthoracic echo, 87% of children had satisfactory sedation with intranasal dexmedetomidine 3 μg/kg (4). The highest published dose of intranasal dexmedetomidine used for procedural sedation is 4 μg/kg for cerebral MRI with no reported negative outcomes (10).

In order to obtain peak plasma levels and the corresponding time after the administration of intranasal dexmedetomidine, an intravenous line of adequate size to allow frequent blood sampling must be placed prior to the administration of the study drug. This is an

unlikely expectation in a pediatric patient. Therefore, we propose administering the drug to the patient already under general anesthesia. We chose the cardiac catheterization population for the following reasons: they require reliable blood drawing access for the procedure that they are undergoing; there is minimal fluid administration, minimal fluid shifts, and the procedures are of adequate duration to obtain several serum samples; and the patients are often administered intravenous dexmedetomidine as part of their anesthetic. Since all patients in the available literature were awake and spontaneously ventilating at the time of intranasal administration of dexmedetomidine and there is no data available which compares the pharmacokinetics of intranasally administered drugs in patients who are spontaneously ventilating with a natural airway versus those that are under general anesthesia with an oral endotracheal tube, we will add additional subjects to our first dosing cohort who are undergoing heart catheterization under sedation with a natural airway and spontaneous ventilation. This additional sub-cohort should allow us to compare the Cmax and Tmax between the 2 populations to ensure that our data in the general anesthesia population can be extrapolated to the awake population.

We are proposing a prospective open-label inter-subject cohort dose-escalation pharmacokinetic study to obtain peak dexmedetomidine drug concentration level in plasma and the corresponding time point following atomized intranasal administration.

1.2 Name and Description of Investigational Product or Intervention



Dexmedetomidine, a selective alpha-2 adrenergic agonist, is indicated for intravenous sedation in the perioperative and intensive care setting. It is currently FDA approved for use as an intensive care unit (ICU) sedative in ventilated adults, and for procedural sedation in spontaneously ventilating adults. Dexmedetomidine is currently not FDA approved in pediatric patients, however based on the literature (11-13), dexmedetomidine 0.5-1 mcg/kg can be administered as a bolus, followed by a continuous infusion at 0.25-2 mcg/kg/hour. After IV administration, the elimination half-life is approximately 2 hours. The intravenous formulation of dexmedetomidine 100 mg/mL will be administered intranasally (non-FDA approved route) to pediatric patients under general anesthesia or sedation undergoing diagnostic or interventional cardiac catheterization. We will be

obtaining serum samples in order to obtain pharmacokinetic data, including maximum concentration, time to maximum concentration, half-life and AUC.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

Not applicable

1.3.2 Clinical Studies

1.3.2.1 Human Pharmacokinetics

To date, there are only 2 studies that evaluate the pharmacokinetics and pharmacodynamics of intranasal dexmedetomidine and both use data from the same six adult male subjects. Iirola and colleagues (1-2) performed a proof-of-concept study to characterize the pharmacokinetics and pharmacodynamics of intranasal dexmedetomidine compared with its intravenous administration in a small number of healthy volunteers. They gave six healthy male volunteers a dose of 84 μg of dexmedetomidine once intravenously and once intranasally via atomizer in a two-period, cross-over design with balanced randomization. The peak plasma concentrations of dexmedetomidine were reached in 38 (15-60) minutes and its absolute bioavailability was 65% (35-93%)(median and range). Pharmacological effects were similar in both routes of administration, but their onset was more rapid after intravenous administration. The authors suggest that dexmedetomidine should be administered intranasally 45-60 minutes prior to the desired moment of maximal effect.

There are no pharmacokinetic studies of intranasal dexmedetomidine in the pediatric patient population. However, the population pharmacokinetics of intravenous dexmedetomine in neonates and infants after open heart surgery has been evaluated by a team at CHOP (14). They performed a prospective dose-escalation trial using 3 cohorts of 12 infants who were enrolled sequentially to 1 of the 3 initial loading dose – continuous IV infusion (CIVI) regimens: 0.35-0.25, 0.7-0.5, and 1-0.75 μg/kg-μg/kg/h. Using the same validated high-performance liquid chromatography-tandem mass spectrometry assay we plan to use, they found that dexmedetomidine clearance increased with weight, age, and single-ventricle physiology, whereas total bypass time was associated with a trend toward decreasing clearance. All dosing regimens were well tolerated in this infant population. They also found in the same dosing cohort that the dexmedetomidine administration provided improved sedation with reduction in supplemental medication requirements, leading to successful extubation (15). This team subsequently looked at cohorts of 9 neonates who similarly received dexmedetomidine administered as a loading dose over 10 minutes followed by a continuous IV infusion for up to 24 hours. The loading doses were the same as in the infant study, however, the infusion doses were 0.2, 0.3, or 0.4 μg/kg/h dexmedetomidine, respectively. They found that dexmedetomidine clearance is significantly diminished in full-team newborns and increases rapidly in the first few weeks of life. In addition to age, they found that dexmedetomidine pharmacokinetics were influenced by weight, total bypass time, and presence of intracardiac shunt (similar to earlier study in infants). They concluded that

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 (16).

1.3.2.2 Clinical Studies in Adults

The clinical use of intranasal dexmedetomidine is quite limited in the adult patient population. Yuen et al (3) used a Koch's design for double-blind crossover trial to evaluate the sedative, anxiolytic, and analgesic effects of dexmedetomine when administered via the nasal route in 18 healthy volunteers between the age of 18 and 38 years. The interventions included a placebo group (A), intranasal dexmedetomidine 1 µg/kg administered via drops from a syringe (B), and intranasal dexmedetomidine 1.5 µg/kg administered via drops from a syringe (C). Intranasal dexmedetomidine was well tolerated and both doses equally produced significant sedation and decreases in bispectral index, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate when compared to placebo ($P < 0.05$). The maximum decreases in SBP were 6, 23, and 21% and in HR were 16, 22, and 26% for Groups A, B, and C respectively. The onset of sedation occurred at 45 minutes with a peak effect at 90-150 minutes. There was no effect on pain threshold, oxygen saturation, or respiratory rate.

1.3.2.3 Clinical Studies in Children

The majority of clinical studies looking at intranasal dexmedetomidine in the pediatric patient population are designed to compare its effectiveness to oral midazolam as a premedication for surgery. Yuen (8) performed the first prospective, randomized, double blind, controlled trial to test the hypothesis that intranasal dexmedetomidine is as effective as oral midazolam for preoperative anxiolysis and sedation in children before induction of anesthesia. They looked at 96 children, aged 2 to 12, scheduled for elective minor surgery. Group M received midazolam 0.5 mg/kg (up to a maximum dose of 15 mg) in acetaminophen syrup and intranasal placebo; Group D0.5 and Group D1 received intranasal dexmedetomidine 0.5 or 1 µg/kg, respectively, and acetaminophen syrup. There were no significant differences in parental separation acceptance, behavior score at induction and wake-up behavior score. When compared with group M, patients in Group D0.5 and D1 were significantly more sedated when they were separated from their parents ($P < 0.001$). Patients from group D1 were significantly more sedated at induction of anesthesia when compared with group M ($P = 0.009$). At the induction of anesthesia, 18.8%, 40.6%, and 53.1% of the children from groups M, D0.5, and D1, respectively, were satisfactorily sedated.

There are 2 additional groups that have performed prospective, randomized, double-blind controlled trials to compare oral midazolam versus intranasal dexmedetomidine for preoperative sedation. Ghali (17) evaluated the preoperative sedative effects, anxiety level changes, and the ease of child-parent separation in 120 children, aged 4 to 12 years, undergoing adenotonsillectomy. For their intervention, the subjects in Group D received intranasal dexmedetomidine 1 µg/kg via drops from a syringe and those in Group M received oral midazolam 0.5 mg/kg (max dose 15 mg) at approximately 60 and 30 minutes, respectively, before induction of anesthesia. Patients premedicated with intranasal dexmedetomidine achieved significantly better sedation levels ($P = 0.042$), lower anxiety levels ($P = 0.036$) and easier child-parent separation ($P = 0.029$) than

children who received oral midazolam. At the time of transferring patients to the OR, the HR was significantly less in the dexmedetomidine group compared to the midazolam group (P = 0.036) and the SBP was significantly less in the dexmedetomidine group compared to the midazolam group (P = 0.032). However, there were no episodes of clinically significant bradycardia, hypotension, hypertension, or desaturation in either group. Segovia and colleagues (5) looked at 108 subjects, aged 2 to 12 years, scheduled for elective surgery. They similarly compared premedication with oral midazolam, 0.05 mg/kg (Group A) versus intranasal dexmedetomidine 1 µg/kg (Group B) . Both interventions occurred 60 minutes prior to the induction of anesthesia. Anxiety was less frequent in the dexmedetomidine group at 60 minutes (p = 0.001), induction (p = 0.04), and recovery (p = 0.0001). Risk assessment showed that dexmedetomidine reduced the risk of anxiety by 28% (RAR = 0.28, 95% CI: 0.12-0.43). Changes in heart rate, mean arterial pressure, and oxygen saturation were statistically significant in the dexmedetomidine group, with no clinical consequences. There were no cases of bradycardia, hypotension or oxygen desaturation.

Two groups have performed prospective, randomized, double-blind controlled trials comparing intranasal dexmedetomidine versus intranasal midazolam as a premedication. Akin and colleagues (18) compared the effects of intranasal dexmedetomidine and midazolam on mask induction and preoperative sedation in 99 children scheduled to undergo adenotonsillectomy. Subjects in Group M received 0.2 mg/kg of intranasal midazolam and subjects in Group D received 1µg/kg of intranasal dexmedetomidine, both via drops from a syringe. They found that satisfactory mask induction was achieved by 82.2% of Group M and 60% of group D (P = 0.01) and that there was no difference between the groups in sedation score (P = 0.36) or anxiety score (P = 0.56) upon separation from parents. Satisfactory sedation was achieved upon separation from parents in 95.5% and 79.9% of patients in the midazolam and dexmedetomidine groups, respectively. Sheta (6) looked at 72 uncooperative children, aged 3-6, undergoing complete dental rehabilitation using the same intervention as Akin but with significantly different results. The median onset of sedation was significantly shorter in group M than in group D [15 (10-25) min vs 25 (20-40) min (P = 0.001)]. Subjects in group D were significantly more sedated than those in group M when they were separated from their parents (77.8% vs 44%, respectively)(P = 0.002). Satisfactory compliance with mask application was 58.3% in group M vs 80.6% in group D (P = 0.035). There were no incidences of bradycardia, conduction abnormalities, hypotension, or respiratory depression in either group.

Two prospective, randomized, double blind, controlled trials have attempted to compare the effects of different doses of intranasal dexmedetomidine to see if the higher dose increased the adequacy of sedation. Yuen (9) compared Dexmedetomidine 1 µg/kg intranasally (group 1) versus Dexmedetomidine 2 µg/kg intranasally (group 2) in 116 children, aged 1 to 8 years, scheduled for elective surgery. 53% of patients in Group 1 and 66% of patients in group 2 were satisfactorily sedated at the time of anesthetic induction. There were no differences in sedation onset time or duration of sedation between the different age groups or the two drug groups. Both doses produced a similar level of satisfactory sedation in children aged 1-4 years, whereas the 2 µg/kg dosing resulted in a higher proportion of satisfactory sedation in children aged 5-8 years. There

were no adverse hemodynamic effects. In 2015, Tug (10) looked at Dexmedetomidine as a sedative for 60 patients, age 1 to 10 years, scheduled for cranial MRI examinations. They used higher doses than any of the other studies: Group 1 received intranasal Dexmedetomidine 3 μg/kg and Group 2 received intranasal Dexdemedetomidine 4 μg/kg. They compared onset time of sedation, mood at separation from parents, imaging quality, MRI duration, rescue anesthetic requirement, total duration of sedation, recovery duration, parents' satisfaction and adverse effects. Rescue anesthetic included placing an intravenous cannula and giving intravenous propofol for the procedure. The parental separation score was significantly higher in Group 2 (P = 0.03). Rescue anesthetic requirement was significantly higher in Group 1 compared to group 2 (70 vs 30%, respectively)(P = 0.002). Neither bradycardia nor oxygen desaturation were observed.

Another study using a higher dose of dexmedetomidine (4) looked at its utility in sedating children for transthoracic echocardiography examination. They gave 115 children under the age of 3 intranasal dexmedetomidine 3 μg/kg administered via atomizer. 87% of children had satisfactory sedation and the mean onset of drug effect was 16.7 ± 7 min (range 5-50 minutes) and the mean wake up time was 44.3 ± 15.1 min (range 12-123 min). The mean age of children who had successful sedation was significantly younger than those who had failed sedation (P <0.001). Four patients had heart rates fall below the age-specific normal ranges. Fifteen children had a systolic blood pressure below the age-specific normal ranges. No intervention was required. This same team (19) looked at an even larger group of children (279 subjects) undergoing transthoracic echocardiography to see if there were any differences in effect when dexmedetomidine was given by an atomizer versus drops from a syringe. To help address the observation they noted in their earlier study that there appeared to be a difference in sedation level based on the age of the subjects, randomization was stratified by age: infants (2-12 months old) and toddlers (>12 months old). They again used intranasal delivery of dexmedetomidine in a dose of 3 μg/kg by either atomizer or drops from a syringe. The successful sedation rate was 82.5% (95% CI 75.3-87.9%) and 84.5% (95% CI 77.7-89.5%) for atomizer and drops, respectively (p = 0.569). Sedation tended to be less successful in older children (p = 0.028, OR 0.949, 95% CI 0.916-0.983). The median sedation onset times, times from onset of sedation until the procedure commenced, duration of procedure, wake-up times and discharge times were no different between the two groups. There were no significant complications.

1.4 Selection of Drugs and Dosages

Dexmedetomidine is a selective alpha-2 adrenergic agonist that is indicated for sedation in the perioperative and intensive care setting, as it has sedative, anxiolytic and analgesic properties. It is available in 4 μg/ml and 100 μg/ml concentrations. For intranasal use, the 100 μg/ml concentration will be used.

Dosing Plan:

Inter-subject cohort dose escalation:

Intranasal Dexmedetomidine 2 μg/kg

Intranasal Dexmedetomidine 4 μg/kg

The dosing of intranasal dexmedetomidine was based on the available clinical data in the pediatric patient population as outlined above. Clinical trials have demonstrated that intranasal dexmedetomidine in a dose of 1 μg/kg and 2 μg/kg produced safe and satisfactory sedation in between 53% and 77% of children at anesthetic induction (6-9). When intranasal dexmedetomidine was used as a primary sedative for transthoracic echo, 87% of children had satisfactory sedation with intranasal dexmedetomidine 3 μg/kg (4). The highest published dose of intranasal dexmedetomidine used for procedural sedation is 4 μg/kg for cerebral MRI which resulted in 76.7% of patients separating easily from their parents with no reported negative outcomes (10). This data would indicate that the 1 ug/kg dose produces a low incidence of satisfactory sedation and that the 2 ug/kg dose has a more acceptable incidence of satisfactory sedation with minimal side effects. There is some data supporting that the 4 μg/kg dose produces a higher incidence of adequate sedation, still with an adequate side effect profile.

The objective of this study is to determine Cmax and associated Tmax. In the adult study of intranasal dexmedetomidine (1) where 84 μg was given, the cmax, average and sd were mean =0.38 ng/ml; sd=0.15 ng/ml; and cv% = 40%. We originally planned to give the following doses: 2 μg/kg, 4 g/kg or 5 or 6 μg/kg. Based on the CV%, differentiating between the doses will be problematic because the upper range of the 2 μg/kg dose (0.644) will fall within the range of the 4 μg/kg dose (0.552-1.288). This comparison would be even more challenging using a 5 μg/kg dose. We have determined that based on an estimated inter-subject variability of 40% for Cmax, a sample size of 21 subjects (7 per group) will be sufficient to detect a difference (alpha 0.05, power 0.8) in Cmax between the three dosing groups if they are given doses of 2,4 and 6 μg/kg.

The older patient population, age >2 yo and ≤ 6 yo, in each dosing cohort will complete enrollment and have PK and safety analysis performed prior to the enrollment of the younger patient population, age ≥1 mo and ≤2 yo. Interim PK and safety analysis will also be performed at the completion of each dosing cohort before enrollment in the next higher dose. The older age group can escalate to the next dosing cohort prior to completing enrollment of the younger age group. An independent Medical Monitor who is an anesthesiologist that is not an investigator on the study will be responsible for assessing and monitoring study safety. Dose-limiting toxicities (DLT) include bradycardia, hypotension, new intraventricular conduction abnormality or any serious adverse event possibly, probably, or definitely related to intranasal dexmedetomidine administration that occurs after the administration of the intranasal dexmedetomidine and through the completion of PK sampling. In particular, bradycardia, hypotension, or new intraventricular conduction abnormalities that occur after the administration of intravenous dexmedetomidine given by the primary anesthesia team as part of usual clinical care will not be considered DLTs. Bradycardia is defined as heart rate <80 BPM in subjects < 1 yo and < 60 BMP in subjects > 1 yo. Hypotension is defined as a mean arterial blood pressure that is >30% lower than baseline. An intraventricular conduction abnormality is defined as second or third degree heart block. Any of these events that cannot be readily explained by the intervention that the patient is undergoing will be

assumed to be related to the effects of the study drug. The clinical team will render an opinion as to whether the hemodynamic change is likely related to intranasal dexmedetomidine.

The maximum tolerated dose (MTD) is defined as the highest dose at which no more than 1 of 7 subjects in a cohort experiences a dose-limiting toxicity OR no more than 1 of 7 subjects in a cohort has a blood level in excess of 1000 pg/mL. This later MTD comes from the intravenous pK data that has been obtained in our studies looking at IV dexmedetomidine administration in infants and neonates undergoing cardiac surgery (14-16). We found that the incidence of bradycardia increased significantly above this concentration level. This MTD was determined with FDA guidance under our current IND (#69758). If a MTD is reached, we will de-escalate the next dosing cohort by 25% of the dose in which the cohort achieved the MTD.

1.5 Relevant Literature and Data

See Section 1.3 for relevant literature.

1.6 Compliance Statement

This study will be conducted in full accordance with all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine the pharmacokinetics of atomized intranasally administered dexmedetomidine in the pediatric patient with congenital heart disease undergoing diagnostic or interventional cardiac catheterization.

2.1 Primary Objective (or Aim)

The primary objective of this study is to determine the peak drug concentration level of dexmedetomidine and the corresponding time of peak concentration level following intranasal administration to the pediatric patient.

2.2 Secondary Objectives (or Aim)

- To perform inter-subject cohort dose escalation of intranasal dexmedetomidine guided by associated dose-limiting adverse events.

- To determine if dexmedetomidine pharmacokinetics are age dependent.
- To determine if dexmedetomidine pharmacokinetics are different when administered intranasally to patients who are spontaneously ventilating versus those that are mechanically ventilated via an oral endotracheal tube.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is a prospective open-label inter-subject cohort dose-escalation pharmacokinetic study. The subjects will receive intranasal dexmedetomidine after the induction of anesthesia or sedation and the placement of intravascular lines to conduct the catheterization. Up to ten serum levels of dexmedetomidine will be obtained by accessing the intravenous lines placed for the heart catheterization. Subjects are age ≥1 mo and ≤ 6 yo undergoing elective diagnostic or interventional cardiac catheterizations.

3.1.1 Screening Phase

The principal investigator will review the Cardiac Center Intake Center appointment schedule approximately 2 weeks in advance of scheduled outpatient procedure. Patients who meet the inclusion criteria will be identified and their charts will be reviewed to determine eligibility. The nurse practitioners in the Intake Center will be notified of potential eligible subjects. On the day of the Intake Center visit, potentially eligible subjects will be approached by one of the physician study team members for enrollment in the study and consent will be obtained. The patient's history will then be reviewed with the family for any exclusion criteria, and if ineligible, the subject will be withdrawn from further study participation. The principal investigator will also review the inpatient procedure schedule one day in advance to identify inpatients who may be eligible for the study. The subject will be approached and consent will be obtained the day before the procedure. Subjects will be recruited into two strata: children ≥1 month up to ≤24 months, and children >2 up to ≤6 years of age with a goal of 50% of subjects per age strata. Parental/guardian permission (informed consent) will be obtained prior to any study related procedures being performed.

3.1.2 Study Treatment Phase (start of the study intervention)

Once consent has been obtained, the patient undergoing general anesthesia will receive premedication at the discretion of the primary anesthesia team caring for the patient. The patient will undergo standard and routine monitoring throughout the heart catheterization procedure as defined by the ASA and the CHOP division of cardiac anesthesia at the direction of the assigned anesthesia providers. Following induction of anesthesia, intravascular access necessary for the heart catheterization will be placed by the interventional cardiologist. The study drug will be obtained from the IDS pharmacy and will be administered via atomizer (Teleflex® LMA® MAD Nasal™ Intranasal Mucosal Atomization Device, MAD300) intranasally by 1 of 2 physician members of the study team. The drug will be administered in one nostril if drug volume is < 1 ml and in both nostrils if total volume is > 1 ml. If the drug volume is > 1 ml, the volume with be split

evenly and administered to both nostrils. No more than 2 ml of study drug will be administered. Serum dexmedetomidine levels will be drawn at approximately 0, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 minutes post drug administration. The 1 mL samples will be drawn by the cardiologist performing the catheterization at the direction of the study team member and will be processed by a study team member. Intraoperative heart rate, rhythm and pulse oximetry will be monitored continuously by the anesthesia team for the duration of the heart catheterization. Blood pressure will be monitored at least every 5 (±3) minutes by non-invasive blood pressure monitoring, and continuously if an arterial line is placed, by the anesthesia team for the duration of the heart catheterization. The attending anesthesiologist may give intravenous dexmedetomidine as a bolus or infusion if desired as part of their normal anesthesia care once the procedure is complete and the intravenous access placed by the interventional cardiologist for the heart catheterization has been removed. At the completion of the procedure, the patient will be transported to the PACU or ICU for recovery. The patient will undergo normal postoperative monitoring and care per standard CHOP CPRU or CICU management. The total duration of monitoring will be for 6 hours from the time of study drug administration.

For the patient undergoing sedation for their cardiac catheterization procedure, the patient will receive sedation by the catheterization lab nurse under the direction of the cardiologist performing the procedure based on CHOP sedation guidelines. The patient will undergo standard and routine monitoring throughout the procedure as defined by the CHOP sedation guidelines. The administration of study drug and drug sampling will be no different than described above and a member of the study team will be present throughout the study duration.

3.2 Allocation to Treatment Groups and Blinding

There is no randomization and there is no blinding.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

Once consent has been obtained, the study duration is for up to 6 hours from the time of drug administration.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at 1 investigative site in the United States.

Recruitment will stop when the following subjects have been enrolled:

Cohort 1A:

- Dexmedetomidine 2 μg/kg
- Under general oral endotracheal anesthesia
- 7 evaluable subjects age >2 yo and ≤ 6 yo
- 7 evaluable subjects age ≥1 mo and ≤2 yo

Cohort 1B:

- Dexmedetomidine 2 μg/kg
- Under sedation with a natural airway
- 7 evaluable subjects age >2 yo and ≤ 6 yo
- 7 evaluable subjects age ≥1 mo and ≤2 yo

Cohort 2:

- Dexmedetomidine 4 μg/kg
- Under general oral endotracheal anesthesia
- 7 evaluable subjects age >2 yo and ≤ 6 yo
- 7 evaluable subjects age ≥1 mo and ≤2 yo

It is expected that approximately 65 subjects will be enrolled to produce 42 evaluable subjects. Evaluable subjects are defined as subjects who received study drug and have completed at least 90 minutes of PK sampling. All subjects who receive study drug will be included in data analysis.

Additional subjects may be required:

- If there is a statistically significant difference in the pharmacokinetics (>30%) between patients who received study drug while under general anesthesia versus those under sedation with a natural airway. If there is a statistically significant difference between Cohort 1A and 1B, we will add a spontaneously ventilating cohort to dosing group 2 as well after IRB and FDA approval. If a statistically significant difference is seen in this group as well, we will request that the remaining dosing cohorts only occur in subjects undergoing sedation with a natural airway.

- For additional dosing cohorts based on defined MTD.

The older patient population, age >2 yo and ≤ 6 yo, in each dosing cohort will complete enrollment and have PK and safety analysis performed prior to the enrollment of the younger patient population, age ≥1 mo and ≤2 yo. Interim PK and safety analysis will also be performed at the completion of each dosing cohort before enrollment in the next higher dose. The older age group can escalate to the next dosing cohort prior to completing enrollment of the younger age group.

3.4 Study Population

3.4.1 Inclusion Criteria

1. Male or female subjects age ≥1 mo to ≤6 yo.
2. Subjects must have congenital heart disease.
3. ASA status 1 to 3.

4. Subjects mechanically ventilated via an oral endotracheal tube scheduled for elective cardiac interventional or diagnostic catheterization anticipated to last ≥ 3hours.
5. Subjects spontaneously ventilating with a natural airway scheduled for elective cardiac interventional or diagnostic catheterization anticipated to last ≥ 2hours.
6. Subjects much have reliable intravascular access from which to draw blood samples.

3.4.2 Exclusion Criteria

1. History of allergic reaction or sensitivity to dexmedetomidine.
2. Nasal pathology preventing the administration of drug.
3. Patients that are on maintenance medications that could inhibit or induce the CYP2A6 enzyme (See Appendix I for full list of CYP2A6 inhibitors and inducers).
4. Cardiac conduction abnormalities defined as second or third degree heart block or pacemaker dependence.
5. Bradycardia, defined by age, upon arrival in the preoperative care area.
6. Hepatic dysfunction defined as a history of hepatic dysfunction and an ALT value greater than 2 times normal in the 6 months prior to study drug administration.
7. The subject has received dexmedetomidine or clonidine within 1 week of the study date.
8. BMI >30.
9. Patients previously enrolled in this study.
10. Any investigational drug use within 30 days prior to enrollment.
11. Wards will not be eligible.

Subjects that do not meet all of the enrollment criteria will not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit

- Informed Consent
- Medical Record Review
- Medication review
- Medication allergy review
- Verification that subject meets study inclusion/exclusion criteria

4.2 Study Treatment Phase

4.2.1 Visit 1

- EKG rhythm strip
- Medical record review
- Dispense study drug
- Administer study drug
- Obtain serum samples at approximately 0, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 minutes from the time of study drug administration.

4.3 Concomitant Medication

All prior and concomitant medications used within 7 days prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.4 Rescue Medication Administration

The subject will be monitored by the primary anesthesia team or the sedation team throughout the entire study period. Hemodynamic management and medication administration will be at the sole discretion of the primary team caring for the patient. At any time, the primary care team may administer medications for the management of hemodynamic perturbations, including bradycardia or hypotension, as clinically indicated. Possible interventions may include the administration of atropine, glycopyrrolate, dopamine or epinephrine. A member of the research team will be present from the time of study drug administration until the study period is complete. Adverse reactions to the study medications will be managed by the clinical team caring for the subject. The teams will not be blinded to study drug administration. Dexmedetomidine is a medication frequently administered by anesthesiologists who are familiar with its use and management. Bradycardia is the most likely effect to be observed.

4.5 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. The Investigator may withdraw subjects to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.5.1 Early Termination Study Visit

Subjects that withdraw from the study will not be evaluable and will not be included in the analysis. No study procedures will be performed following subject withdrawal.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

- Date of procedure
- Date of birth
- Age
- Weight
- Height
- Gender
- Race, ethnicity
- American Society of Anesthesia (ASA) Physical Status
- Physical examination
- Scheduled catheterization procedure
- Catheterization procedure performed
- Allergies
- Medical history
- Single or double ventricle physiology defined
- Current medications
- ECG within 6 months if available
- Premedication administered (drug, dose and route) if applicable
- Duration of anesthesia
- Duration of cardiac catheterization
- Dose of dexmedetomidine provided for post procedure sedation, if applicable
- Intraoperative heart rate, rhythm and pulse oximetry will be monitored continuously by the anesthesia team or the sedation team for the duration of the heart catheterization.

- Blood pressure will be monitored at least every 5 (±3) minutes by non-invasive, automated blood pressure monitoring, and continuously if an arterial line is placed, by the anesthesia team or sedation team for the duration of the heart catheterization.

5.1.2 Vital Signs

While the patient is lying down for the procedure:

- EKG rhythm prior to the administration of the study

5.2 Pharmacokinetic Evaluation

Samples of 0.5 -1 ml of blood, totaling less than 1 tablespoon of blood, will be drawn at approximately 0, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 minutes from the time of intranasal drug administration. Once invasive monitoring lines have been removed, samples will only be collected if either vascular access that permits blood draws exists or

a scheduled phlebotomy is performed for clinical indications and the subject has not received intravenous dexmedetomidine as part of their normal anesthesia care. Dexmedetomidine plasma concentration will be determined using a selective and highly sensitive, validated high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay used for analysis of pediatric plasma with a lower limit of quantitation of 5 pg/mL (20). The assay will be performed in an academic laboratory setting and clinical decisions will not be made based on the results. Plasma will be separated by centrifugation and stored at -80° C. Dexmedetomidine will be extracted from 200 microliters of plasma by solid-phase extraction. Method validation will be performed according to guidelines set by the United States Food and Drug Administration (FDA) for bioanalytical method validation (21). Based on prior experience with this assay (20) this method will again be validated in terms of linearity, specificity, lower limit of quantitation (LLOQ), recovery, intra- and inter-day accuracy and precision, and stability of analyte during the sample storage and processing procedures. Each analytical run will include blanks, nine standard concentrations for calibration, and replicate sets (n = 6) of QC samples (LQC, MQC and HQC).

Samples will be run in batch following each dosing cohort and the data will be analyzed. One- and 2-compartment models will be investigated. The model deemed optimal to define the dexmedetomidine plasma concentration profile based on the results from the model-building process will be used.

Investigators will adhere to the NIH "Guidelines for Limits of Blood Drawn for Research Purposes" which states that for pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day and no more than 9.5 mL/kg may be drawn over any eight-week period.

5.3 Safety Evaluation

Patients will be monitored by continuous heart rate and rhythm monitoring, continuous oxygen saturation monitoring, and at least every 5 (±) minute SBP, DBP and mean BP monitoring by automated non-invasive blood pressure monitoring. If an invasive arterial line is placed, continuous blood pressure monitoring will occur. Continuous ECG monitoring will be conducted to evaluate for evidence of cardiac ischemia. Ischemia is defined as widened Q-waves (>0.035 seconds) or new T-wave inversion. This monitoring will continue for the duration of the heart catheterization. At the completion of the procedure, the patient will be transported to the PACU or ICU for recovery. The patient will undergo normal postoperative monitoring and care per standard CHOP CPRU or CICU management. The total duration of monitoring will be for 6 hours from the time of study drug administration.

Interim PK and safety analysis will be performed at the completion of each dosing cohort before enrollment in the next cohort. The older patient population, age >2 yo and ≤ 6 yo, in each dosing cohort will complete enrollment and have PK and safety analysis performed prior to the enrollment of the younger patient population, age ≥1 mo and ≤2 yo. An independent Medical Monitor who is an anesthesiologist that is not an investigator on the study will be responsible for assessing and monitoring study safety.

In this particular clinical setting, a number of the research subjects will receive usual clinical care IV dexmedetomidine for sedation management in addition to the initial research IN dexmedetomidine. AEs may occur in some subjects early, following the administration of research IN drug and during sample collection, prior to administration of usual clinical care IV dexmedetomidine. AEs may also occur later in some subjects, following the usual clinical care intravenous dexmedetomidine (and well after the initial IN dexmedetomidine). In this latter circumstance, the medical monitor will adjudicate whether the AE is attributable to IN dexmedetomidine, or whether IN dexmedetomidine contributed to the AE resulting after usual clinical care dexmedetomidine. In both circumstances (following initial research IN drug, and later, following both research IN as well as usual clinical care drug) AEs will be reported as either unlikely, possibly, probably or likely related to the research IN dexmedetomidine.

Dose-limiting toxicities (DLT) include bradycardia, hypotension, new intraventricular conduction abnormality, or any serious adverse event possibly, probably, or definitely related to intranasal dexmedetomidine administration that occur after the administration of the intranasal dexmedetomidine and through the completion of PK sampling. In particular, bradycardia, hypotension, or new intraventricular conduction abnormalities that occur after the administration of intravenous dexmedetomidine given by the primary anesthesia team as part of usual clinical care will not be considered DLTs. Bradycardia is defined as <80 BPM in subjects < 1 yo and <60 BPM in subjects > 1yo. Hypotension is defined as a mean arterial blood pressure that is >30% lower than baseline. New intraventricular conduction abnormality is defined as second or third degree heart block. The MTD is defined as the highest dose at which no more than 1 of 7 subjects in a cohort experiences a dose-limiting toxicity OR no more than 1 of 7 subjects in a cohort has a blood level in excess of 1000 pg/mL. This later MTD comes from the intravenous pK data that has been obtained in our studies looking at IV dexmedetomidine administration in infants and neonates undergoing cardiac surgery (14-16). We found that the incidence of bradycardia increased significantly above this concentration level. This MTD was determined with FDA guidance under our current IND (#69758). If a MTD is reached, we will de-escalate the next dosing cohort by 25% of the dose in which the cohort achieved the MTD.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint of this study is to determine the peak drug concentration (Cmax) of inhaled dexmedetomidine and the corresponding time of peak concentration (Tmax) following intranasal administration to the pediatric patient with congenital heart disease.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- Compare dexmedetomidine pharmacokinetics between two age ranges receiving the same intranasal dexmedetomidine dosing.
- Compare dexmedetomidine pharmacokinetics in patients who received the intranasal dose while spontaneously ventilating versus those that are mechanically ventilated via an oral endotracheal tube to see if there is a difference in absorption.
- To perform inter-subject cohort dose escalation of intranasal dexmedetomidine guided by associated dose-limiting toxicities.

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

6.3.2 Pharmacokinetic/Pharmacodynamic Analysis

Description of pharmacokinetic parameters to be assessed and methods to be employed to calculate those parameters:

Nonparametric analytical methods will be used due to small sample sizes that are not uniformly distributed, to compare the Cmax and Tmax between age groups, and also between spontaneous breathing subjects and those that are mechanically ventilated.

The PK of dexmedetomidine is well described. Bayesian parameter estimates from prior studies will be used to perform a two-compartment open model with first-order elimination from the central compartment to fit to the concentration-time data from all evaluable subjects. This approach will allow for a model-based approach to determine the PK parameters of this population in the event that our sampling does not extend past one half life (120 minutes) for some subjects.

Comparisons between pharmacodynamics measures before receiving dexmedetomidine and following the administration of intranasal dexmedetomidine will be made using each patient as his/her own control. These comparisons will be stratified by individual dosing cohorts as well as the entire population collectively. The following pharmacodynamics measures will be evaluated: HR, heart rhythm SBP, DBP, and MAP. A Wilcoxon signed rank test will be used for comparison of continuous variables at baseline and after the administration of intranasal dexmedetomidine for approximately 6 hours.

The following pharmacodynamics measures will be compared between dosing cohorts following the administration of intranasal dexmedetomidine: HR, SBP, DBP, and MAP.

The following variables will be assessed for correlation with plasma concentration: HR, heart rhythm, SBP, DBP, and MAP. Nonparametric Spearman rank correlation will be used to evaluate the correlation of variables to plasma concentrations.

Plasma concentration will be assessed for correlation with anesthetic method (ie, sedation in the spontaneously ventilating patient versus general oral endotracheal intubation) in the first dosing cohort. If a greater than 30% difference in plasma concentration is seen between these 2 populations, the following dosing cohort will expand to include patients who are both spontaneously ventilating versus those receiving general oral endotracheal intubation. If a greater than 30% difference in plasma concentration is again seen, the remaining dosing cohorts will only occur in patients who are under sedation and spontaneously ventilating at the time of drug administration.

6.3.3 Safety Analysis

All subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.4 Sample Size and Power

The primary objective of this study is to determine the Cmax and corresponding Tmax after the administration of intranasal dexmedetomidine. The sample size is based on this objective. In the adult study of intranasal dexmedetomidine (1) where 84 μg was administered, the cmax, average and standard deviation were mean = 0.38 ng/ml; sd 0.15 ng/ml; and cv% = 40%. Based on an estimated inter-subject variability of 40% for Cmax, a sample size of 21 subjects (7 per group) will be sufficient to detect a difference (alpha 0.05, power 0.8) in each age cohort. Fourteen evaluable patients will be enrolled at each dose group. An additional 14 patients will be added in the first cohort to see if there is any difference in the pharmacokinetics of a patient who is under general anesthesia with an oral endotracheal tube versus a patient who is spontaneously ventilating at the time of intranasal drug administration. Based on heart catheterization lab patient census, it is estimated that 15 months will be required to complete enrollment.

6.5 Interim Analysis

Interim PK and safety analysis will be performed at the completion of each dosing cohort before enrollment in the next higher dose. The older patient population, age >2 yo and ≤ 6 yo, in each dosing cohort will complete enrollment and have PK and safety analysis performed prior to the enrollment of the younger patient population, age ≥1 mo and ≤2 yo. An independent Medical Monitor who is an anesthesiologist that is not an investigator on the study will be responsible for assessing and monitoring study safety.

Dose-limiting toxicities (DLT) include bradycardia, hypotension, new intraventricular conduction abnormality, or any serious adverse event possibly, probably, or definitely related to intranasal dexmedetomidine administration that occur after the administration of the intranasal dexmedetomidine and through the completion of PK sampling. In particular, bradycardia, hypotension, or new intraventricular conduction abnormalities that occur after the administration of intravenous dexmedetomidine given by the primary anesthesia team as part of usual clinical care will not be considered DLTs. Bradycardia is defined as heart rate <80 BPM in children <1 yo and a heart rate <60 BPM in subjects > 1 yo. Hypotension is defined as a mean arterial blood pressure that is >30% lower than baseline. A new intraventricular conduction abnormality is defined as second or third degree heart block. The MTD is defined as the highest dose at which no more than 1 of 7 subjects in a cohort experiences a dose-limiting toxicity OR no more than 1 of 7 subjects in a cohort has a blood level in excess of 1000 picograms/mL (14-16). If a MTD is achieved, the next dosing cohort will be at a dose 25% lower than the cohort at which the MTD occurred.

7 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

7.1 Description

Dexmedetomidine is a selective alpha-2 adrenergic agonist that is indicated for sedation in the perioperative and intensive care setting, as it has sedative, anxiolytic and analgesic properties. At the cellular level, dexmedetomidine binds to an alpha-2 adrenergic receptor. After binding to the receptor, there is a subsequent decrease in calcium influx to the cell and increase in potassium efflux from the cell, thereby decreasing the action potential of the neuron. This results in membrane hyperpolarization, decreasing the chances of it firing, which decreases norepinephrine release. Ultimately this elicits the pharmacologic action, a hypnotic response pattern that mimics the natural sleep pathway. After administration, patients are effectively sedated but are still easily arousable. By decreasing sympathetic activity, the effect is decreases in blood pressure and heart rate, sedation and anxiolysis. Binding of dexmedetomidine to alpha-2 adrenergic receptors in the spinal cord results in analgesia.

7.1.1 Packaging

Dexmedetomidine is supplied as a 100 μg/mL solution (2 mL). The study drug will be obtained from Pfizer pharmaceuticals.

7.1.2. Labeling

Dexmedetomidine vials will be clearly marked with their contents from the original manufacturer. They will be dispensed from the CHOP Investigational Drug Service in accordance with FDA guidelines with a patient specific label immediately prior to the procedure. An example of the label will be included with the IND application submission to the FDA.

7.1.3 Dosing

Administration of intranasal dexmedetomidine has been reported in the literature with doses ranging from 1-4 μg/kg/dose. For the purposes of a pharmacokinetic analysis in pediatric patients and determination of a maximum tolerated dose, dexmedetomidine 2 μg/kg/dose, 4 μg/kg/dose and 6 μg/kg/dose (based on interim analysis) will be administered to patients undergoing cardiac catheterization. Dexmedetomidine will be administered intranasally via the Teleflex® LMA® MAD Nasal™ Intranasal Mucosal Atomization Device, MAD300 (See Attachment) which will be used as directed and instructed by the CHOP clinical pharmacy. This atomizer is currently approved for use at CHOP. The drug will be administered in one nostril if drug volume is < 1 ml and in both nostrils if total volume is > 1 ml. If the drug volume is > 1 ml, the volume with be split evenly and administered to both nostrils. No more than 2 ml of study drug will be administered. The drug will be administered by 1 of 2 physician members of the research study to provide consistency in administration. Since the patients will be under general anesthesia or moderate sedation at the time of administration, issues such as sneezing should be limited. If there should be a concern with the quality of administration in a given patient, the data would still be collected and interpreted in the context of the administration concerns.

We chose to us an atomizer as opposed to drops because it produces fine particles of drug that are thought to optimize drug absorption, hasten onset, and provide more efficient sedation (22,23). Li and colleagues (19) compared intranasal delivery of dexmedetomidine in a dose of 3 mcg/kg by either atomizer or drops from a syringe in children less than 3 years old undergoing transthoracic echocardiography. They found both modes of administration equally effective. This has also been seen with the administration of ketamine and midazolam, (24,25) supporting the concept that the drug could be administered effectively by either technique. However, these studies also found improved patient acceptance of the drug when administered by atomizer. Also, larger volumes of drug administration when given by dropper technique may lead to partial oral administration making the PK data difficult to interpret. Oral dexmedetomidine has poor oral bioavailability (26). Finally, the one adult study that looked at intranasal PK data (1) used an atomizer for administration.

7.1.4 Treatment Compliance and Adherence

Medications will be administered in the operating room and each subject's participation will last for up to 6 hours from the time of drug.

7.1.5 Drug Accountability

Adequate records of study drug receipt and disposition will be maintained by the CHOP Investigational Drug Service (IDS), including records of receipts, investigational drug orders, dispensing records, and disposition forms that will be examined during the course of the study. Dexmedetomidine lot number and expiration date will be included in the IDS records. The purpose of these records is to ensure regulatory authorities and the Sponsor that the investigational new drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the Investigator or designee and may not be used for any purpose other than that described in this protocol. At the completion of each subject, all drug supplies will be wasted in a hospital approved drug disposal box and witnessed by 2 members of the study team. Drug supplies include partially used or empty vials as well as used atomizers. At study completion, all remaining unused drug will be destroyed in accordance with CHOP IDS policies.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) and study stopping criteria will be monitored throughout the study.

8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

TABLE 2: CAUSALITY CATEGORY DEFINITIONS

Causality Term	Assessment Criteria
Definitely/ Certain	• Event abnormality with plausible time relationship to drug intake • Cannot be explained by disease or other drug or intervention • Response to withdrawal plausible (pharmacologically, pathologically)
Probably/ Likely	• Event abnormality with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drug or intervention • Response to withdrawal clinically reasonable
Possibly	• Event abnormality with reasonable time relationship to drug intake • Could also be explained by disease or other drug or intervention • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event abnormality with time to drug intake that makes a relationship improbable (but not impossible)

	• Disease or other drug provide plausible explanations

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Investigator Reporting Requirements to Sponsor

The PI will promptly notify the Sponsor of all unexpected fatal or life-threatening events that are related to the research activity within 24 hours by telephone or by email. A follow-up email will be provided to the Sponsor within 48 hours of the event and a PDF document of this email exchange will be created and stored electronically. Other unexpected, non-life threatening SAEs related to the research involving risk to the subjects or others will also be reported by the PI to the Sponsor via email within 48 hours of the event and a PDF document of this email exchange will be created and stored electronically. All other SAEs that are determined by the PI to not be related to the study intervention and non-serious AEs will be reported to the Sponsor at the monthly research meetings.

8.7 FDA Notifications of SAEs/IND Safety Reports to the FDA

(Refer to 21 CFR 312.32)

Any unexpected fatal or unexpected life-threatening event that occurs while the subject is on study and is determined by the PI to possibly be due to investigational drug administration, will be reported to the FDA as soon as possible, but no later than 7 calendar days after the PI has been notified of the event.

Unexpected, non-life-threatening SAEs that occur while the subject is on study, and are determined by the PI to be due to investigational drug administration, will be reported to the FDA as soon as possible but no later than 15 calendar days after PI has been notified of the event.

All other SAEs that are determined by the PI to be not related to the study intervention and non-serious AEs will be reported to the FDA at or by the time of the Annual Report.

8.8 Study Stopping Criteria

The study will be stopped and reassessed if any of the following criteria are met:

- A single adverse event requiring unanticipated admission to the hospital
- Greater than 20% of subjects experiencing hypotension as defined by 30% decreased in blood pressure from baseline.
- Greater than 10% of subjects experiencing severe hypotension as defined by 50% decreased from baseline and that requires treatment beyond fluid replacement with IV isotonic solution.
- Greater than 20% of subjects experiencing bradycardia as defined as heart rate <80 BPM in children <1 yo and a heart rate <60 BPM in subjects > 1 yo and/or requiring rescue medications such as atropine, glycopyrrolate, epinephrine or dopamine that the practitioner attributes to the administration of study drug.
- One subject who experiences a serious adverse event, with serious adverse event defined as death, life-threatening adverse event (e.g. cardiac arrest), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Stopping criteria, just like adverse events, will be assessed continuously, starting with the first patient enrollment and until study completion.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

Not applicable.

9.2 Data Collection and Management

Data will be collected and recorded by the PI and co-investigators. The inpatient chart and patient records contained within EPIC systems will be reviewed for relevant data. The information will be recorded in an electronic database.

1. Confidentiality. A master list containing PHI and subject ID number will be kept separate from data forms (paper and electronic) that have only a study ID number. The master list will be on a separate computer. This form of data is considered "coded" not de-identified. As long as the data can be re-linked to identifiers, the data is coded. Only when the key to the code or the Master List is destroyed are the data considered de-identified.

2. Security. A copy of the password-protected file will be kept on the primary investigators office computer and the original will be kept in one of the Hospital's secure servers.

3. As this is an FDA-regulated study, data collected from this study will be destroyed 2 years after a marketing application has been approved or 2 years after all research of the study has been completed, and as approved by the Sponsor, and in accordance with all local policies regarding data retention.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with institutional policies and HIPAA on subject privacy and investigators will not use such data and records for any purpose other than conducting the study. Safeguards are described under "9.2 Data Collection and Management."

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

The study will be monitored by the sponsor and co-investigators. Prior to trial initiation, trial readiness will be confirmed by the Office of Research Compliance (ORC) of CHOP, as assessed by the Pre-Trial Monitoring Visit. Periodic institutional monitoring will also be conducted according to ORC guidelines.

After enrolling and starting administration of the investigational agent to the first subject, the sponsor (or CHOP PI) will contact the ORC to arrange a monitoring visit. Thereafter, ORC will monitor the study at least annually.

The principal investigator will be responsible for data safety. Information will be collected from patient blood sampling and the anesthesia record in EPIC and will be

stored in a password protected electronic database. Access to this database will only be granted to members of the study team. Safety signals requiring reporting to the IRB and FDA will be submitted according to whether the reporting is expedited (in the event of serious adverse events) or non-serious, which will be reported as part of the IRB continuing review and FDA annual report, as outlined in protocol Section 8.

An independent Medical Monitor who is an anesthesiologist that is not an investigator on the study will be responsible for assessing and monitoring study safety. Interim PK and safety analysis will be performed at the completion of each dosing cohort before enrollment in the next higher dose.

9.4.2 Risk Assessment

Risks during this study are considered a minor increase above minimal risk. Patients undergoing these procedures regularly receive dexmedetomidine intravenously as part of their anesthetic. Attending anesthesiologists or the sedation team administering the study-assigned analgesic(s) will not be blinded and will be able to manage side-effects or complications accordingly, which is consistent with how side effects or complications would be managed when these medications are administered in routine clinical practice. Study interventions other than administration of the study drug include data collection and medical chart review. An additional risk to subjects in this study is the potential loss of confidentiality that would occur if identifiable subject information were to be distributed to those not authorized to access it. This is highly unlikely to occur as only the master list will contain any identifiable subject information, and the identifiable information will be limited to the subject's name, medical record number, date of birth and date of the procedure. The master list will be kept in a password-protected file in one of the Hospital's secure servers and a backup copy of this password-protected file will be kept on the principal investigator's password-protected office computer.

9.4.3 Potential Benefits of Trial Participation

There are no direct patient benefits. However, the results of this study could provide potential future guidance for use of intranasal dexmedetomidine as pre-procedure anxiolysis in pediatric patients.

9.4.4 Risk-Benefit Assessment

Risks during this study are considered a minor increase above minimal risk. Patients undergoing these procedures are often exposed to dexmedetomidine intravenously. Defining the pharmacokinetics of intranasal dexmedetomidine may benefit future patients at CHOP and other institutions. For these reasons the potential benefits to study subjects and future patients coupled with no significant increased risk favor both trial participation for subjects and conduct of the trial.

9.5 Recruitment Strategy

The principal investigator will review the Cardiac Center Intake Center appointment schedule approximately 2 weeks in advance of scheduled outpatient procedure. Patients

who meet the inclusion criteria will be identified and their charts will be reviewed to determine eligibility. The nurse practitioners in the Intake Center will be notified of potential eligible subjects. On the day of the Intake Center visit, potentially eligible subjects will be approached by one of the physician study team members for enrollment in the study and consent will be obtained. The patient's history will then be reviewed with the family for any exclusion criteria, and if ineligible, the subject will be withdrawn from further study participation. The principal investigator will also review the inpatient procedure schedule one day in advance to identify inpatients who may be eligible for the study. The subject will be approached and consent will be obtained the day before the procedure.

Subjects will be recruited into two strata: children ≥1 month up to ≤24 months, and children >2 up to ≤6 years of age with a goal of 50% of subjects per age strata. Parental/guardian permission (informed consent) will be obtained prior to any study related procedures being performed.

9.6 Informed Consent/Assent and HIPAA Authorization

Eligible subjects will be approached by one of the physician study members for enrollment in the study. For outpatients, consent will take place in the Cardiac Center Intake Center. For inpatients, consent will take place in the subject's hospital room. If subjects are unsure if they would like to consent to the study at this initial meeting, they will be re-approached the day of their scheduled procedure for potential participation. The discussion and consent will outline the purpose of the study, including that the subject will not have a direct benefit from the drug administration and that risks during this study are considered to be a minor increase above minimal risk. Subjects will also be informed that their decision to participate or not in the study will in no way affect their care. Subjects/families will sign a combined consent-authorization document.

9.6.1 Waiver of Assent

Waiver of assent is requested for all subjects in this study based on their ages. No child 7 years old or older is eligible for enrollment, and therefore subjects will not have the capability to be consulted for assent.

9.7 Payment to Subjects/Families

There will be no payment to subjects or families for study participation.

10 PUBLICATION

After collection, review, and analysis of data, the results of this study will be submitted for publication in a peer-reviewed scientific journal. The study will only be conducted at CHOP, and the PI will have access to all data. Anticipated time of submission is 18 months after the start of the study

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APPENDIX I

CYP2A6 Inhibitors and Inducers

CYP2A6 Inhibitors	CYP2A6 Inducers
Amiodarone	Barbiturates
Amlodipine	Rifampin
Desipramine	
Fenofibrate	
Isoniazid	
Ketoconazole	
Gabapentin	
Pilocarpine	
Pregabalin	
Selegiline	