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OFFICIAL TITLE:

An observer-blinded randomized study of propofol infusion vs bolus dexmedetomidine and propofol sedation for pediatric magnetic resonance imaging

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PURPOSE OF THE STUDY

This study is designed to compare the efficacy of low-dose dexmedetomidine and propofol with a continuous2infusion of propofol for outpatient magnetic resonance imaging scans performed on children ages 12 months to 60 months. The primary outcome to be measured is the efficiency of the techniques utilized as measured by time required to establish adequate conditions for scanning, time to eye opening, spontaneous movement and readiness for discharge from the department to home or clinic. Secondary outcomes include frequency of airway obstruction and oxygen desaturation, and hemodynamic changes associated with initiation and maintenance of sedation. Any medications required for completion of the study will be compared between the groups. In addition, the total drug administered will be calculated. Data regarding parental satisfaction and post-procedural behavioral and sleep disturbances will be collected.

HYPOTHESIS / SPECIFIC AIMS

We hypothesize that low-dose dexmedetomidine and propofol in combination provide satisfactory conditions for diagnostic MRI imaging with reduced time to arousal and readiness for discharge when compared to continuous infusion of propofol.

BACKGROUND, SIGNIFICANCE, AND RATIONALE

Magnetic resonance imaging is utilized with increasing frequency in the diagnosis and management of pediatric disease. Unlike other imaging techniques, these studies require a significant amount of time for completion, ranging from thirty minutes to several hours. Most young children are incapable of remaining immobile for the duration of the scan and require sedation and/or anesthesia for a successful study. A number of sedation models have been described in the literature and are reviewed here. The use of barbiturates, chloral hydrate, propofol, dexmedetomidine, ketamine, benzodiazepines, opioids and inhalational anesthetic agents will be reviewed.
In December 2016, the FDA announced new warnings regarding the use of general anesthetics and sedation drugs in young children. (https://www.fda.gov/Drugs/DrugSafety/ucm532356.htm) which include all of the drugs listed with the exception of dexmedetomidine.

> *Published studies in pregnant animals and young animals have shown the use of general anesthetic and sedation drugs for more than 3 hours caused widespread loss of nerve cells in the brain. Studies in young animals suggest these changes result in long-term effects on the animals' behavior or learning (see Data Summary).*[1-20] *Studies have also been conducted in children,*[21-43] *some of which support findings from previous animal studies, particularly after repeated or prolonged exposure to these drugs early in life. All the studies in children had limitations, and it is unclear whether any negative effects seen in children's learning or behavior were due to the drugs or to other factors, such as the underlying medical condition that led to the need for the surgery or procedure.*

In response, Dean Andropoulos observed that "There are no alternatives to these general anesthetic drugs for children younger than 3 years of age. . . . The only other drugs in clinical use for sedation and anesthesia that do not cause neurodegeneration in animal models are dexmedetomidine and opioids, but these agents are not sufficient for general anesthesia and do not represent a feasible option by themselves."[1] Sedation failures are common when performed by sedation teams or radiologist supervised nurses, necessitating general anesthesia to complete the studies at a later date. Prolonged sedation and behavioral issues following the scan maybe problematic.

The safety of propofol administered by intensivists and emergency medicine physicians for MRI procedures is well documented for patients as young as one month of age both in-hospital and at free-standing imaging centers.[2,3] Total propofol doses published in the literature range from approximately 7 mg/kg to 12 mg/kg. Mallory et al[4] reviewed 7079 sedations comparing propofol to pentobarbital and found that although apnea occurred more often in patients receiving propofol, the rate of airway complications was not significantly different. Increased sedation failure, unplanned admission, prolonged recovery and vomiting were more common among patients receiving pentobarbital.

Kiera Mason et al[5] demonstrated the safety of high dose dexmedetomidine administered by non-anesthesiologists despite the occurrence of hypertension, hypotension and bradycardia. Typical dosing strategies were 2-3 mcg/kg load followed by 1-2 mcg/kg/hour maintenance. Siddappa et al[6] found that despite its excellent safety profile, recovery is prolonged, and additional medications, are required to maintain immobility in a significant number of patients. A recent article by Boriosi[7] suggests that a combination of propofol and dexmedetomidine results in a reduced number of adverse events, particularly upper airway obstruction and oxygen desaturations when compared to propofol alone. All patients in this cited study received a single dose of oral midazolam 0.3-0.5 mg/kg prior to PIV placement. In the prop-dex combination group the mean dose of propofol administered was 9 mg/kg compared to 12 mg/kg for propofol alone. Furthermore, animal studies suggest that dexmedetomidine may actually have *neuroprotective effects* by reducing cerebral ischemia-induced oxidative stress and apoptosis.[8]

With concern for delayed awakening following diagnostic imaging procedures, we began to evaluate the effectiveness of low-dose polypharmacy to reduce recovery time and adverse behavioral changes. In a QI study conducted in 2014, we observed that for procedures lasting less than one hour, 1 mcg/kg/hr dexmedetomidine in combination with 1-2 mg/kg propofol at the onset of sedation is effective for successful diagnostic imaging. In addition to the rapid arousal and discharge, the total drug requirement with this strategy is markedly less than that published in the literature for propofol alone.

We aim to conduct a randomized, observer-blinded study to compare the low-dose sedation strategy now commonly used by the anesthesia providers at Children's Hospital of Wisconsin with propofol alone for pediatric patients undergoing imaging procedures. Outcome measures in addition to the improved efficiency and time to discharge will include total drug dose administered, frequency of airway obstruction and oxygen desaturation, and hemodynamic changes associated with initiation and maintenance of sedation. Any additional medications required for completion of the study will be compared between the groups.

DESIGN AND METHODS

Forty outpatients scheduled for elective MRI evaluation will be randomized to receive either propofol (Group Prop) as a continuous infusion or a low-dose propofol and dexmedetomidine combination (Group PropDex) to establish adequate sedation. All out-patients ages 12 months to 72 months will be eligible for enrollment. Exclusion criteria are inpatient status, airway abnormalities, allergy to any study medications, eggs and soy, and mitochondrial disorders. All subjects with any cardiac disease or history of cardiac arrhythmias will be excluded.
Patients will be randomized to receive either PropDex or Prop by the research pharmacist utilizing Research Randomizer an online computer-based random number generator. An investigator will be blinded to the drugs selected. He/She will observe the airway manipulations and obtain hemodynamic data during the first ten minutes of the procedure. The observer will be blinded to the drugs administered.
ASA guidelines regarding procedural sedation will be followed. All patients will be screened for MRI safety, and a focused history and physical examination including neurological, airway, head and neck, respiratory and cardiovascular systems will be obtained on the day of the procedure. All patients will receive an intravenous infusion of lactated Ringer's or a dextrose containing solution for replacement and maintenance fluids as determined by the anesthesia provider. Patients will be anesthetized with sevoflurane and nitrous oxide if necessary for intravenous access at the discretion of the anesthesiologist. Otherwise, j-tip lidocaine will be utilized to anesthetize the insertion site. Parental presence will be permitted during induction if judged to be in the best interest of the patient. Midazolam syrup 0.3 mg/kg may be administered at the discretion of the treating anesthesiologist. This is not a part of the study protocol.

MONITORING

Monitoring includes videocamera, direct visual observation, electrocardiogram, blood pressure, heart rate, respiratory rate and end-tidal CO_2
The treating anesthesiologist will monitor the patient during the initiation of sedation. Once a stable depth of moderate sedation (Ramsey 3) is established the sedation nurse will monitor and record HR, O2 sat, end tidal CO2. Initial blood pressure measurements will be obtained at time 0, 2, 4, 6 and 10 minutes following initial administration of study drugs. Blood pressure will then be obtained every 5 minutes throughout the procedure for all patients in the propofol infusion arm and for any PropDex patients who require infusion of propofol to complete the imaging study. Patients in the PropDex group will have blood pressure measurements obtained every fifteen minutes after the first 10 minutes except when additional drugs are administered or if the blood pressure is not stable and is decreasing at which time the monitoring interval will be every five minutes or more frequently until stable blood pressures are recorded. The blood pressure monitor interval will be in compliance with the current clinical standard of care at Children's Hospital of Wisconsin and adjusted to comply with standard care at the discretion of the anesthesiologist caring for the patient.

STUDY PROTOCOL

Group Prop

- Peripheral intravenous (IV) placed following j-tip lidocaine local anesthesia or inhalation induction with sevoflurane and nitrous oxide
- Lactated Ringers or other intravenous solution, type and volume infused to be determined by anesthesiologist providing care
- Loading dose propofol 2 mg/kg after administration of 1 mg/kg lidocaine IV

- 0.25 ml/kg/hr normal saline infused over 5 minutes; (see table below) This saline administration is the placebo/replacement for the dexmedetomidine administered to Group PropDex
-

Scan Duration	30	45	60	75
Saline dose	0.125 ml/kg	0.2 ml/kg	0.25 ml/kg	0.3 ml/kg
Duration of saline administration	5 minutes	5 minutes	5 minutes	5 minutes
Propofol loading dose	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg
Propofol infusion	200mcg/kg/min	200 mcg/kg/min	200mcg/kg/min	200mcg/kg/min
• propofol infusion rate 200 μ/kg/min for 30 minutes, then decreased to 150 mcg/kg/min if no movement • administer 1 mg/kg propofol and increase propofol infusion by 50 mcg/kg/min for movement up to 300 μ/kg/min				

Group PropDex

- Peripheral intravenous (IV) placed following j-tip lidocaine local anesthesia or inhalation induction with sevoflurane and nitrous oxide
- Lactated Ringers volume infused to be determined by anesthesiologist providing care
- Loading dose propofol 2 mg/kg after administration of 1 mg/kg lidocaine IV

Scan Duration	30	45	60	75
Dexmedetomine dose (4 μ/ml soln)	0.5 mcg/kg	0.7 mcg/kg	1 mcg/kg	1.25 mcg/kg
Glycopyrrolate dose	4 mcg/kg	4 mcg/kg	4 mcg/kg	4 mcg/kg
Duration of administration loading dose	5 minutes	5 minutes	5 minutes	5 minutes
Propofol loading dose	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg
Propofol infusion	None	None	None	None
Dexmedetomidine infusion	None	None	None	None
• propofol 1 mg/kg for patient movement or administration of contrast • begin propofol infusion at 150 mcg/kg/min if second bolus propofol required to complete study				

At the completion of the MRI scan patients will be transported to MRI recovery area for continued monitoring until awake, are taking appropriate oral or enteral feeds and baseline neurological function is observed.

STATISTICAL ANALYSIS

Sample size was estimated using previously reported discharge times following propofol sedation for MRI procedures and a thirty percent reduction in discharge times when low-dose dexmedetomidine and propofol are administered. Wu[9] reported a recovery time of 35.7 ± 10.8 following propofol infusion at 200 $\mu \cdot kg^{-1} \cdot min^{-1}$, resulting in a standardized difference of 0.97. Sample size is calculated to be 40 patients when a power of 0.80 and a significance level of 0.05 is applied.

Demographic, time, and physiologic measures are summarized by count and percent, mean and standard deviation, or median and interquartile range if measures fail skewness or kurtosis tests of normality. Baseline group characteristics are compared by standardized differences, and measures were compared by Fisher exact, two-sample t, or Kruskal-Wallis equality of rank tests. Times to recovery measures are compared by log-rank tests with Kaplan-Meier graphical display of decay function. Phases of case are grouped into discrete epochs, during which physiologic measures are electronically collected at 2-5 minutes intervals. Repeated physiologic measures are analyzed using maximum likelihood cross-sectional panel regression on independent variables of treatment group and epoch, with variance adjusted for repeated measures within subject, and identity or log-link functions to satisfy normality criteria. Scheffe's adjustment for multiple contrasts are applied to tests of differences between groups across epochs and within groups from baseline. Significance for all tests will be $p<0.05$. Analysis will be performed with Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).\

DRUGS OR PROCEDURES

Medications to be used in this study:

1. Propofol is approved for use as an anesthetic agent in patients 2 months of age and older.
2. Glycopyrrolate is recommended by the FDA to be used with propofol when other agents or surgical stimulation may increase the risk of bradycardia. (Propofol package insert)
3. Lidocaine is approved for use in children. The FDA recommends administration of lidocaine immediately prior to propofol injection to reduce the pain associated with injection of the drug. (Propofol package insert)
4. Sevoflurane is approved for use in all pediatric patients.
5. Nitrous oxide is approved for use in all pediatric patients.
6. Dexmedetomidine is not approved for use in children. However, the drug is used routinely for sedation and as an adjunct to general anesthesia at CHW and other institutions caring for children. A detailed review of safety data and the justification for Off-Label and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices is presented in Appendix A

RISK CATEGORY:

(2) 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

RISKS AND THE PRECAUTIONS WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE

All anesthetic procedures involve risk to the patient. The goal of anesthesia is to produce a loss of consciousness and awareness of sensation. Changes in breathing, even apnea, and alterations in hemodynamics are expected consequences of anesthesia. The drugs and procedures in this study are known to be associated with the following risks:

Anesthetic Risks in this research study			
Peripheral IV	Pain	Very likely	Not serious
	Infection	Very unlikely	May be serious
	Bruising	Likely, if IV is difficult	Not serious
	Injection outside of the vein	unlikely	Not serious with drugs used in this study
Medications			
Propofol	Pain with injection	Very likely	Not serious
	Low blood pressure	Very likely	Not serious; usually still normal
	Decreased breathing	Likely	Not serious if treated immediately
	Allergic reaction	Very unlikely	May be very serious
	Unusual movements during anesthesia	Very unlikely	Not serious; does not continue after the drug is stopped
	Continued sleepiness	Very likely	Not serious. Limit activity after study
Dexmedetomidine	Low heart rate	Very likely	Not serious
	High blood pressure	Likely if given too fast	May be serious
	Low blood pressure	Very likely	Not serious; usually still "normal"
	Continued sleepiness	Very likely at higher doses	Not serious;
Lidocaine	Reactions rare when given as a single dose; most side effects are overdoses		
	Ringing in ears	unlikely	Not serious
	Metallic taste	unlikely	Not serious
	Seizure	Very unlikely	May be serious
	Heart rhythm changes	Extremely unlikely	May be very serious

Glycopyrrolate	Most side effects are seen with repeated higher doses		
	Dry mouth	Likely	Not serious
	Fast heart rate	Likely	Not serious
	High or low blood pressure	Very unlikely	May be serious
Inhalation induction of anesthesia for peripheral IV placement			
Sevoflurane	Nausea and vomiting	Unlikely in children younger than 3 years	May be serious if severe and unable to drink liquids
	Nausea and vomiting	More common in older children; unlikely following short exposure	May be serious if severe and unable to drink liquids
	Cough	Somewhat likely	May be serious
	Fast heart rate	Likely	Not serious
	Slow or difficult breathing	Likely	May be serious; an anesthesia provider will help your child breathe to prevent serious side effects
	Agitation after procedure	Likely	Not serious, but may be unpleasant for caregivers; the child is not aware when this happens
Nitrous oxide	Nausea and vomiting	Unlikely in young children	May be serious (unlikely) when unable to drink liquids
MRI scan	Allergy to contrast dye	Very unlikely	May be very serious
	Skin burn	Very unlikely	Somewhat serious
	Loud noise, hearing damage	Extremely unlikely	Not serious

Rescue Maneuvers for Individual Anesthetic Risks

The MRI department consists of 3 magnets with a central work area. Each machine has a dedicated anesthesia machine, ventilator, suction equipment, and full non-invasive monitoring capabilities. Additional airway equipment, including ambu bag, intubating equipment and endotracheal tubes are located in an anesthesia cart stationed in the control room (Zone 3). Anesthesia and resuscitation drugs are also located in the cart. Specific interventions for each anesthesia drug are listed below.

Dexmedetomidine		
Adverse reaction	Definition	Rescue Maneuvers
Hypotension	30% decrease Systolic BP from pre-study level	Lactated Ringers 10cc/kg Decrease or stop drug administration Phenylephrine 1-2mcg/kg

		Trendelenburg position
Respiratory depression	> 30 % decrease respiratory rate from pre-study level	Stimulation Jaw thrust Bag and mask ventilation
Bradycardia/sinus arrest	Decrease 30% from pre-study level	Observation if not symptomatic Glycopyrrolate 2 mic/kg IV Stop dexmedetomidine infusion Stop other medications that affect sinus node Glycopyrrolate or atropine Pressor agents
Transient Hypertension	30 % increase BP from pre-study level	Reduce loading infusion rate
Nausea		Ondansetron 0.15 mg/kg IV
Post-marketing adverse events reported in pediatric patients (~250,000 patients 0-11 years)*		
Syncope (3 cases)[1]		Bedrest until Ramsey 5; up with assistance
Agitation/neuropsych[1]	Unable to Console, no eye contact	Quiet environment
Tolerance,tachyphylaxis	Not applicable to this study	Seen after > 24 hour administration

* IMS Health Inpatient Healthcare Utilization System (IHCarUS). June 2010-May 2015. File: Precedex Adhoc Nov 18 2015

[1]Reported events occurred following administration of much larger doses of dexmedetomidine than will be administered in this study.

Propofol		
Adverse Event		Rescue
Cardiovascular	Bradycardia[1]	Glycopyrollate if symptomatic
	Arryhthmia	
	Tachycardia	
	Hypotension[1]	Decrease or stop infusion rate, IV lactated Ringer's 10 cc/kg, phenylephrine
	Hypertension[1]	Stop administration of drug
CNS	Uncontrolled athetoid movement	Stop drug administration; administer alternative sedation; terminate study
Injection site	Burning	Increase rate of administration; prior administration of lidocaine as recommended by FDA attenuates this effect
Respiratory	Apnea	Jaw thrust, baag
Allergic reaction	Rash Anaphylaxis	Discontinue drug; IV fluids, diphenhydramine, epinephrine; airway and cardiovascular support as needed

[1]Definitions as described in Dexmedetomidine Table above.

Lidocaine		
Adverse Event	Definition	Rescue
Tinnitus	Ringing in ears	Stop administration of drug; Symptomatic treatment; reassurance
Seizure	Generalized shaking	Stop drug administration Maintain patent airway and assist ventilation as needed Administer propofol or benzodiazepine to stop seizure
Arrhythmia/cardiac arrest	HR < 60, ventricular ectopy; ventricular tachycardia or fibrillation; asystole	Stop drug administration Cardiopulmonary resuscitation Intralipid emulsion 20%

Sevoflurane		
Adverse event	Definition	rescue
Bradycardia	<30% dec pre-study heart reate	Decrease concentration of agent; glycopyrrolate if needed
Hypotension	<30% dec pre-study systolic blood pressure	Decrease sevoflurane, administer lactated ringer's
Tachycardia	Transient increase on induction up to 50% above baseline	Decrease sevoflurane concentration

Nitrous Oxide		
Hypoxia	O2 sat < 90%	Increase O2 concentration of delivered gases
Nausea		Keep NPO; administer IV fluids; ondansetron

Patients in the propofol group will be receiving routine care and the risk level is minimal as the study will only involve data collection. Patients in the prop/dex group will have the additional risks of receiving dexmedetomidine and glycopyrrolate. These risks are listed above and include hyper- and hypotension, bradycardia and sedation. Glycopyrrolate will be given with dexmedetomidine to attenuate the degree of bradycardia known to occur. The FDA recommends administration of an anticholinergic agent with the administration of propofol when it is used with other agents that may cause bradycardia. Dry mouth is associated with administration of glycopyrrolate but at the dose administered the symptoms should be minimal.
Anesthetic risks will be minimized by following CHW and ASA guidelines for sedation and anesthesia. This will include

- Administration of anesthesia by providers board certified in pediatric anesthesia
- Appropriate monitoring including videocamera, direct visual observation, electrocardiogram, blood pressure, heart rate, respiratory rate and end-tidal CO_2

We will follow standard CHW safety protocols regarding MRI, that include

- scanning patients for ferromagnetic materials prior to entering the scanner
- utilization of MRI compatible equipment and monitors
- Videocamera for continuous observation of patient to readily recognize movement
- Noise – earplugs and headphones
- Patients at risk for renal disease will have appropriate laboratory studies performed prior to administration of gadolinium whose major route of excretion is renal.
- For additional information, Please refer to the Children's Hospital of Wisconsin policy and procedure guidelines for procedural sedation. Appendix A

CONFIDENTIALITY PROVISIONS

All paper records are kept in locked cabinets in the anesthesiology department, with restricted access. Only de-identified information is stored. Each subject will be assigned a study

identification number. The legend associating the study number with the patient medical record number will be stored securely by the pharmacy department. Data analysis will be performed on a MCW secure server.

ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY

For patients randomized to the prop/dex group we anticipate that significantly reduced doses of anesthetic agents will be administered for MRI studies in small children. These subjects may benefit from a more rapid recovery from the procedure. Significantly reduced dosing of both propofol and dexmedetomidine may reduce the adverse events and side effects that may be seen when either drug is used alone. Because of poorly understood but ongoing concerns for the potential adverse outcome on behavior and learning in children exposed to anesthetic agents, both the subjects recruited and future patients will benefit from the results of this study. Subjects in the propofol group will be treated with a medication that routinely provides conditions satisfactory for successful MRI imaging necessary for the diagnosis and treatment of their diseases. There may be no additional benefit to the patients assigned to this group**.**

STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

Individual subject stopping criteria include:

- Sinus or junctional bradycardia below 30% of preoperative heart rate or requiring rescue medications or treatments
- Any cardiac arrhythmia (with the exclusion of sinus tachycardia or sinus bradycardia that resolves without intervention) before the initiation of dexmedetomidine infusion
- Junctional rhythm sustained for greater than 15 minutes, or requiring rescue medications or treatments, or associated with greater than 30% decrease in mean arterial pressure (MAP) from preoperative baseline value
- Onset of second or third degree heart block, regardless of necessitating an intervention
- Hypotension defined ad 30% decrease in MAP from preoperative baseline value
- Cardiac arrest or any other life-threatening event

Events that would serve as criteria for stopping the study include:

- A single adverse event requiring unanticipated admission to hospital following sedation for MRI scan
- Greater than 20% of subjects experiencing hypotension as defined by 30% decrease from baseline
- Greater than 10% of subjects experiencing severe hypotension as defined by 50% decrease from baseline and that requires treatment beyond fluid replacement with IV isotonic solution
- Greater than 20 % of subjects experience bradycardia as defined as heart rate below 30% of pre-study heart rate that requires rescue medications.

Stopping criteria will be assessed continuously starting with the first patient enrolment and until study completion.

We anticipate that the study will be completed after the successful recruitment of 70 patients. Because we are studying the procedures currently in place at CHW that have been employed safely and successfully for the past three years we do not anticipate safety concerns other than those inherent in sedation and anesthetic techniques utilized in the care of children. We are aware

that randomization to study groups may present potential unanticipated risks to subjects. Analysis of the data prior to completion of the study demonstrating significant differences in primary outcomes between groups would be grounds for early termination of the study.

DATA SAFETY MONITORING BOARD

The principal investigator will review the data obtained every two weeks to ascertain whether unintended adverse outcomes have occurred. All adverse events will be assessed continuously, starting with the first patient enrollment and until study completion. Any serious adverse event will be reported to the IRB as required. In addition, if preliminary review of the data suggests that differences in the primary outcomes are significant prior to enrolling 70 subjects, the study will be terminated at that time.

Severity Grading of Adverse Events

	Mild	Moderate	Severe	Life-threatening
Peripheral IV Pain	Does not interfere with activity	Requires non-narcotic analgesia	Requires narcotic analgesia	ER visit
Infection	Resolves with topical antibiotic therapy	Requires oral antibiotics	Requires IV antibiotics	Hospital admission
Bruising	Does not interfere with activity	Requires non-narcotic analgesia	Requires analgesia Interferes with activity	Hospital admission
Infiltration	2.5-5 cm does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Propofol				
Pain on injection	See above			
Hypotension[1]	Transient decrease to 40% below pre-study level	Transient dec to 50% below pre-study level; no intervention	Sustained dec to less than 30% pre-study level; requires volume resuscitation	Sustained hypotension to less than 50% pre-study level requiring inotropic support
Hypoventilation[2]	Transient decrease in respiratory rate to less than 12; no intervention	Decrease in Respiratory rate or minute ventilation requiring assisted bag and mask ventilation for > 2 min	Sustained decrease in respiratory rate or minute ventilation with associated hypoxia to O2 sat < 85% for > 30 seconds	Decrease in ventilation requiring intubation and prolonged ventilation
Allergic Reaction	Hives; symptomatic Decrease propofol treatment	Bronchospasm requiring bronchodilator therapy with hypotension	Bronchospasm and cardiovascular compromise requiring epinephrine	Sustained reaction requiring ongoing inotropic support and hospital admission
Athetoid movements	Involuntary movements ; resolves with discontinuing drug	N/A	N/A	N/A

Prolonged sedation after discontinuing drug	>60 minutes unresponsive to verbal response	> 90 min unresponsive to verbal response	>90 minutes unresponsive to physical stimulation	Requires hospital admission

[1]Decrease in blood pressure to levels 30% of awake values is an expected outcome of propofol anesthesia
[2]Transient hypoventilation and/or apnea are expected results of induction of anesthesia with Propofol

Dexmedetomidine				
Bradycardia[1]	HR <35% below pre-drug level; normal BP, ET CO2	HR < 40% below pre-drug level, normal BP, ETCO2	HR < 50% below pre-drug level; requires anticholinergic	Sustained bradycardia < 50% pre-drug requiring hospital admission
Hypertension[2]	BP > 40% above pre-drug level; no therapy	BP>60% above pre-drug level; resolves within 5 minutes without therapy	BP> 70% above pre-drug level; resolves within 5 minutes; may require intervention	Sustained BP > 50% above pre-drug level requires ongoing therapy and hospital admission
Hypotension[3]	Transient dec to 30% below pre-study level (<5 min)	Transient dec to 40% below pre-study level; no intervention (<5min)	Sustained dec to less than 40% pre-study level; requires volume (>5 min) resuscitation	Sustained hypotension to less than 50% > 10 min pre-study level requiring inotropic support
Prolonged sedation after discontinuing drug	>45 minutes unresponsive to verbal response	> 60 unresponsive to verbal response	>60 minutes unresponsive to physical stimulation	Requires hospital admission
Lidocaine[4]	Tinnitus, metallic taste; no intervention	Seizure; resolves spontaneously or with benzodiazepine	Cardiac arrhythmia and seizure	Cardiac arrest requiring CPR; intraipid therapy
Glycopyrrolate	Dry mouth	Tachycardia, agitation	Central anticholinergic syndrome (2 case reports since 1991) Resolves with physostigmine	Central Anticholinergic syndrome (2 case reports since 1991) Sustained, requires hospitalization
hypotension	Reported to be associated with benzoyl alcohol in neonates. Not seen in older patients			

[1]Bradycardia in adult clinical trials defined as < 40 beats/min or < 30% pre-study drug level. Pediatric HRs vary by age and frequently "baseline" values are obtained in agitated crying patients.
[2]Hypertension is generally self-limited and attenuated by slow administration of bolus.
[3]Hypotension defined in adult clinical trials as <30% pre-study infusion value, systolic pressure <80, diastolic <50
[4]These side effects are observed at higher lidocaine doses, generally > 5 mg/kg unless intra-arterial injection results in high brain concentrations of the drug. Even tinnitus would not be expected at the drug doses for this study.

Sevoflurane				
Nausea and vomiting	Nausea, resolves spontaneously, able to take oral liquids	Nausea; unable to take liquids;	Nausea and vomiting; requires	Nausea and vomiting sustained

		resolves with antiemetic therapy	IV hydration and antiemetic therapy	requiring hospital admission
Airway irritability	Transient cough	Mild laryngospasm resolves with positive pressure ventilation	Laryngospasm requiring succinylcholine to resolve	Sustained airway irritability requiring hospital admission
Hypoventilation				
Emergence delirium	Post-procedure delirium lasting < 10 minutes; resolves spontaneously	Post-procedure delirium lasting > 20 minutes; resolves spontaneously	Post procedure delirium resulting in physical harm to patient	Post procedure delirium requiring hospital admission

Nitrous Oxide	Nausea, resolves spontaneously, able to take oral liquids	Nausea; unable to take liquids; resolves with antiemetic therapy	Nausea and vomiting; requires IV hydration and antiemetic therapy	Nausea and vomiting sustained requiring hospital admission

M 2. Causality Definitions

Causality term	Assessment criteria
Certain	• Event with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Adverse reaction • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

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