

Propofol Sedation for Longitudinal Pediatric Neuroimaging Research

Laurie B. Amundsen, MD,* Alan A. Artru, MD,* Stephen R. Dager, MD,†‡ Dennis W. W. Shaw, MD,†
Seth Friedman, PhD,† Bobbi Sparks, BA,† and Geraldine Dawson, PhD§

Abstract: There is disagreement about allowing propofol sedation for research magnetic resonance imaging/spectroscopy (MRI/MRS) in children. Our study is the first to provide relevant safety and efficacy data. With institutional approval, 108 research MRI/MRS procedures under propofol sedation were performed longitudinally on children at ages 3–4 years (N = 59) and 6–7 years (N = 49). Sedation parameters, physiological values, and outcome data were collected. Success rate for acquisition of satisfactory quality MRI/MRS during propofol sedation was compared with that in typically developing, age-matched sleeping children. Only 5 minor events (2 with need to insert an oral airway, 2 with premature termination of study, 1 with bradycardia not requiring treatment) and no major events occurred. These safety/efficacy data are equal to or better than previously reported with propofol for clinically indicated procedures. A high percentage of parents of children participating in MRI/MRS studies at 3–4 years of age returned with their child at 6–7 years of age, and longitudinal follow-up was not adversely impacted by their child's experience with sedation. The success rate of data acquisition was significantly higher during propofol sedation (98%) than during late-night sleep studies in typically developing children (30%–50%). We conclude that propofol sedation for research MRI/MRS is safe and effective when children of appropriate ASA class are selected, supplemental oxygen is delivered, and sedation and monitoring are done by an experienced anesthesiologist.

Key Words: MRI, pediatric neuroimaging, propofol, safety, sedation
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In current neuroanesthesia practice there is widespread acceptance of the use of propofol to sedate children for clinically indicated neurodiagnostic procedures such as magnetic resonance imaging (MRI).¹ In such circumstances, the acquisition

of MRI information is judged to be of such benefit to the patient's care that any potential risk associated with propofol sedation is more than offset by the benefit. This use of propofol is supported by an extensive literature on the safety and effectiveness of propofol for clinical sedation/anesthesia in children without major cardiovascular disease having procedures that were noninvasive or invasive, and diagnostic or therapeutic.^{2–32}

In contrast, there is considerable disagreement regarding the use of propofol to sedate children for research neuro-radiologic procedures such as MRI and magnetic resonance spectroscopy (MRS). Some have judged the risk to be minimal and believe the potential benefit of the research results more than offset the potential risk. Those making the opposite judgment question the safety/utilization of sedation in general, and propofol in particular, prompting prohibition, for research neuroimaging purposes, of propofol sedation in certain agencies in the United States (such as National Institute of Mental Health) and throughout other countries (such as Canada).³³ Data relevant to this disagreement are sparse. Only limited data are available on the safety and effectiveness of propofol for diagnostic MRI (7 reports, 3 with no outcome data and 4 with incomplete outcome data), and there are no reports on the safety or effectiveness of propofol for research MRI/MRS.^{9,10,17,25,28,30,32}

Administration of propofol to and monitoring of children having diagnostic and therapeutic procedures at our institution are based on practice guidelines of the University of Washington Department of Anesthesiology and the above-mentioned body of literature on propofol sedation/anesthesia in children. Since 1997 we have used propofol for sedation of young children undergoing MRI/MRS studies for research purposes. Our expectation was that adopting the same guidelines for sedation of children undergoing research MRI/MRS as for clinically indicated procedures should insure safe anesthetic care, an experience that was well tolerated by the children and their parents, successful completion of the MRI/MRS procedure, and uneventful recovery, so that a high proportion of parents would be willing to bring their children back to continue participating in our longitudinal imaging research. A further consideration in our choice of propofol is that it increases seizure threshold, similar to some but not all sedative agents, a useful characteristic for sedation of children with autism spectrum disorder (ASD) who are at high risk of seizures (up to 38%).³⁴

To date, we have completed 2 stages of an ongoing longitudinal research project investigating brain developmental processes associated with ASD and idiopathic developmental delays (IDD). The aim of the present study was to report our

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From the *Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington; †Department of Radiology, University of Washington School of Medicine, Seattle, Washington; ‡Departments of Psychiatry and Bioengineering, University of Washington School of Medicine, Seattle, Washington; and §Department of Psychology, University of Washington School of Medicine, Seattle, Washington.

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Reprints: Alan A. Artru, MD, Department of Anesthesiology – 356540, University of Washington School of Medicine, Seattle, WA 98195-6540 (e-mail: artruaa@u.washington.edu).

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safety/outcome measures, compare them to previously reported data, and to compare our imaging success in our groups of propofol-sedated children to that in a group of sleeping "control" children with typical development.

MATERIALS AND METHODS

With institutional review and approval from the University of Washington Human Subjects Committee, written informed consent was obtained from parents or legal guardians before their child's participation. A total of 108 MRI/MRS studies (59 at ages 3–4 years and 49 at ages 6–7 years) were performed in ASD/IDD children sedated with propofol, and physiological values were monitored and recorded. In addition, 26 MRI/MRS studies were performed in children with typical development for comparison with the studies in ASD/IDD children. Additional demographic and diagnostic details, procedural and recruitment strategies, and inclusion/exclusion criteria are presented in the Appendix.

Fasting was required for all children before the procedure, as recommended by the American Society of Anesthesiologists (ASA).³⁵ Specifically, solid food (including milk) was withheld for at least 8 hours in children over 36 months of age, but clear liquids were allowed up to 3 hours before the procedure. The care team included a pediatric nurse, 3 physicians (anesthesiologist, psychiatrist, and pediatric neuro-radiologist), and a PhD imaging researcher. Before the procedure, 1 of the physicians evaluated each child: fasting was verified, a medical history was taken, a physical examination was performed, and the use of medications was noted, as were the existence of allergies, details of previous sedation, and adverse reaction to anesthesia by the child or a blood relative. The physical examination included an evaluation of the airway and auscultation of the heart and lungs. Additional data recorded included the child's name, age, weight, gender, and diagnosis. If the child did not meet strict fasting criteria or presented with symptoms or history consistent with upper respiratory tract infection, ie, history of coughing at night, "runny nose," or congested breath sounds at auscultation, the procedure was rescheduled.

In a room adjacent to the scanner and, generally, with the child sitting in his/her parent's lap chest-to-chest, venous access was established by the pediatric nurse. Propofol was given immediately in incremental doses of 1.0–1.5 mg/kg initially with additional bolus doses of 0.5–1.0 mg/kg to achieve loss of consciousness with continued spontaneous ventilation. A solution of 5% dextrose in 0.25% saline was infused at 4 mL/kg/h. After the initial dose of propofol was given, an automated, noninvasive blood pressure cuff was placed (usually on the lower leg), a pulse oximeter was placed (on either a finger or a toe), and supplemental oxygen was supplied by face mask at 4 L/min. Sedation was maintained by continuous infusion of propofol using a starting dose of 200 μ g/kg/min and titration of the dose based on usual clinical indicators such as blood pressure, pulse rate, respiratory rate, and movement. The child and bed were moved into the scanner room, and the child's head was placed into a dedicated, specially built, pediatric linear birdcage coil for MRI/MRS.^{36,37} 3-Dimensional coronal imaging sets were acquired as well as 2-D multiecho axial series to

allow tissue classification with the coregistered MRS acquisition. MRS was performed using a 2-D spectroscopic imaging technique, proton echo planar spectroscopic imaging (PEPSI) acquired at 2 echo times and at 2 spatial levels in conjunction with water scans for tissue-based chemical quantification.³⁸ Soft supports were placed under the child's head, neck, and shoulders so as to position the child with the head forward and neck slightly extended. Nasal prongs were placed for monitoring of expired carbon dioxide tension and respiratory rate. These data were considered along with the above-mentioned data to guide the titration of the propofol infusion and additional propofol boluses as needed.

Noninvasive blood pressure was measured at 2.5-minute intervals, and pulse rate and regularity, oxyhemoglobin saturation, respiratory rate, and expired carbon dioxide tension were measured continuously and recorded at 5-minute intervals by the anesthesiologist, who remained in the scanner room. We carefully noted the occurrence of any signs of discomfort, movement, inadequate sedation, airway obstruction, apnea, adequacy of capillary perfusion, cyanosis, nausea, vomiting, agitation, and whether the procedure was accomplished successfully. Also recorded were the need for interventions such as those for maintaining airway patency (eg, repositioning of the head, insertion of an oral or nasal airway, bag-and-mask assisted ventilation, and endotracheal intubation) or blood pressure.

At the conclusion of the procedure, the infusion of propofol was discontinued, and the child and bed were removed from the scanner room to the recovery area, where the child rejoined his/her parent(s). Monitoring with noninvasive blood pressure and pulse oximetry and delivery of supplemental oxygen continued until the child was nearly recovered from sedation and monitoring was no longer indicated. The time from the child's entry to the recovery area until the time the family left the recovery area was noted, as was the success rate for acquisition of satisfactory quality MRI/MRS. The 3 physicians on the care team were available 24 h/d to address questions, concerns, and possible complications.

Statistical Analysis

Data on patient characteristics, initial propofol dose, propofol infusion rate, subsequent bolus propofol doses, oxyhemoglobin saturation, systolic and diastolic blood pressures, pulse rate, respiratory rate, and expired carbon dioxide tension were summarized as mean \pm SD. For data recorded at intervals (propofol infusion rate, oxyhemoglobin saturation, blood pressure, pulse rate, respiratory rate, and expired carbon dioxide tension), the mean and SD were calculated for each 15-minute interval (ie, 0–15, 16–30, 31–45, ... and 166–180 minutes). Data on occurrence of hypoxia, airway obstruction, repositioning of the head for airway obstruction, instrumentation of the airway because of airway obstruction, apnea, bag-and-mask ventilation for apnea, hypotension, bradycardia, tachycardia, irregular pulse, inadequate capillary perfusion, cyanosis, nausea, vomiting, agitation, major negative outcome, and premature termination of the procedure are presented as incidence. Hypoxia was defined as oxyhemoglobin saturation less than 90%. The airway was considered to be partially obstructed if snoring was heard, retraction

of respiratory muscles was observed, or an expiratory plateau was not observed on the capnography trace. Apnea or complete airway obstruction was defined as no breath for more than 10 seconds. For mean systolic blood pressure within each 15-minute interval, a mean systolic blood pressure less than 30% of baseline systolic blood pressure was considered to represent hypotension. The critical values for bradycardia and tachycardia were 80 beats/min and 120 beats/min, respectively, for the 3- to 4-year-old age group and 75 beats/min and 115 beats/min, respectively, for the 6- to 7-year-old age group.^{39,40} Quantitative data on expired carbon dioxide tension and respiratory rate were not available for children in the 6- to 7-year-old age group as a result of the capnometer being relocated away from the effects of the magnetic field within the scanner room, to behind a glass partition separating the scanner room from the scanner control room (where the capnometer was monitored by another care team physician).

The success rate for acquisition of satisfactory quality MRI/MRS in our ASS/IDD children was compared with that in our typically developing children using the χ^2 test. The rate of occurrence of major events (eg, hypoxia, apnea, significant hypotension, poor perfusion/cyanosis, severe cardiac dysrhythmia, and major negative outcome) for the aggregate data from this study and previous reports was compared for fac-

tors that may have affected those rates using the Fisher exact test.²⁻³² $P < 0.05$ was considered statistically significant.

RESULTS

In the 3- to 4-year-old age group, the mean age was 47.6 ± 4.5 months. The mean weight was 18.6 ± 4.2 kg. There were 43 boys and 16 girls. Fifty-eight children were classified as ASA class 1, and 1 child was classified as ASA class 2. The mean initial dose of propofol was 3.07 ± 1.16 mg/kg ($n = 59$ children), and the mean dose of the subsequent bolus doses was 0.90 ± 0.28 mg/kg ($n = 2$ children). Complete interval data depended on the length of the individual exams and generally were available for all children for 0–90 minutes, >95% of children for 95–105 minutes, and >83% of children for 110–120 minutes. For time periods longer than 120 minutes, complete interval data were present in fewer than half of the children because of earlier completion of the MRI/MRS procedure. Table 1 displays the interval data for 0–120 minutes for this age group. The range of individual propofol infusion rates was 180–220 $\mu\text{g}/\text{kg}/\text{min}$. Notable events were recorded for all children regardless of the duration for which complete interval data were available. There were only 4 notable events (Table 2). The incidence of notable events was: partial airway

TABLE 1. Physiological Values in 3- to 4-Year-Old Children

	0–15 min	16–30 min	31–45 min	46–60 min	61–75 min	76–90 min
ETCO ₂ (mm Hg)	40.1 ± 8.1 N = 59	40.0 ± 8.2 N = 59	40.6 ± 7.9 N = 58	41.1 ± 8.3 N = 58	41.5 ± 8.4 N = 57	41.6 ± 8.4 N = 57
sPO ₂ (%)	93.5 ± 12.8 N = 59	96.1 ± 2.0 N = 59	96.6 ± 2.1 N = 59	96.8 ± 2.0 N = 59	96.9 ± 2.1 N = 58	97.1 ± 2.1 N = 58
Systolic blood pressure (mm Hg)	99.7 ± 8.5 N = 59	95.1 ± 8.1 N = 59	93.8 ± 7.9 N = 59	93.1 ± 7.9 N = 59	93.2 ± 8.4 N = 58	93.9 ± 9.2 N = 58
Diastolic blood pressure (mm Hg)	44.5 ± 5.3 N = 59	38.4 ± 4.3 N = 59	35.8 ± 4.6 N = 59	34.9 ± 4.7 N = 59	34.6 ± 5.2 N = 58	35.0 ± 5.6 N = 58
Heart rate (beats/min)	94.9 ± 7.0 N = 59	91.7 ± 8.5 N = 59	90.4 ± 9.4 N = 59	89.5 ± 8.7 N = 59	88.7 ± 9.2 N = 58	88.3 ± 8.1 N = 58
Respiratory rate (breaths/min)	16.9 ± 2.7 N = 59	19.5 ± 3.5 N = 59	19.5 ± 4.0 N = 59	19.1 ± 3.9 N = 59	19.3 ± 4.0 N = 58	19.0 ± 3.6 N = 58
Propofol infusion rate ($\mu\text{g}/\text{kg}/\text{min}$)	200.7 ± 11.81 N = 59	204.3 ± 17.1 N = 59	203.3 ± 15.8 N = 59	200.9 ± 16.9 N = 59	200.4 ± 17.4 N = 58	199.9 ± 17.26 N = 58
	91–105 min	106–120 min	121–135 min	136–150 min	151–165 min	
ETCO ₂ (mm Hg)	41.6 ± 9.1 N = 55	40.8 ± 9.0 N = 48	43.6 ± 9.3 N = 22	44.9 ± 9.3 N = 8	42.5 ± 6.4 N = 2	
sPO ₂ (%)	97.4 ± 2.0 N = 56	97.5 ± 1.9 N = 50	97.9 ± 1.5 N = 26	97.6 ± 1.9 N = 10	97.0 ± 1.4 N = 2	
Systolic blood pressure (mm Hg)	95.9 ± 8.5 N = 56	98.5 ± 9.7 N = 53	99.0 ± 11.1 N = 32	99.1 ± 10.8 N = 13	98.0 ± 11.3 N = 2	
Diastolic blood pressure (mm Hg)	36.3 ± 5.6 N = 56	37.8 ± 6.2 N = 53	38.1 ± 6.6 N = 32	40.7 ± 8.5 N = 13	44.5 ± 0.7 N = 2	
Heart rate (beats/min)	88.4 ± 8.2 N = 56	88.4 ± 9.8 N = 53	89.0 ± 8.8 N = 31	88.4 ± 8.7 N = 11	98.3 ± 0 N = 1	
Respiratory rate (breaths/min)	19.0 ± 3.3 N = 56	19.1 ± 3.3 N = 53	18.7 ± 3.4 N = 31	18.5 ± 3.4 N = 14	19.7 ± 0.5 N = 2	
Propofol infusion rate ($\mu\text{g}/\text{kg}/\text{min}$)	201.2 ± 20.8 N = 56	200.1 ± 21.5 N = 53	202.2 ± 27.1 N = 32	201.2 ± 28.1 N = 14	150.0 ± 0 N = 2	

ETCO₂, expired carbon dioxide tension; sPO₂, oxyhemoglobin saturation.

TABLE 2. Notable Events

Event	Incidence at Age 3–4 Years, Present Study	Incidence at Age 6–7 Years, Present Study	Overall Incidence, Present Study	Incidence Range Among Previous Studies
Partial respiratory obstruction	2/59	0/49	1.9%	0–17%
Tachycardia	0/59	0/49	0%	0–0.5%
Bradycardia	1/59	0/49	0.9%	0–6%
Study terminated	1/59	1/49	1.9%	NA
Hypoxia	0/59	0/49	0%	0–30%
Apnea	0/59	0/49	0%	0–20%
Hypotension	0/59	0/49	0%	0–68%
Poor perfusion/cyanosis	0/59	0/49	0%	0%
Severe cardiac dysrhythmia	0/59	0/49	0%	0%
Major negative outcome	0/59	0/49	0%	0%
Nausea/vomiting	0/59	0/49	0%	0–32%
Agitation	0/59	0/49	0%	0–8%

Tachycardia, heart rate >100 beats/min; bradycardia, heart rate <60 beats/min; NA, data not available; hypoxia, oxyhemoglobin saturation <90% (in most reports; several reports used other critical value; range of critical values was 85%–95%); apnea, no breath for >10 seconds; hypotension, systolic blood pressure decrease of >30% from baseline or to below the fifth percentile for age (in most reports); severe cardiac dysrhythmia, irregular, fast, or slow pulse rate accompanied by hypotension.

obstruction in 2/59 (treated by insertion of an oral airway), bradycardia in 1/59 (not requiring treatment), and premature termination of the study in 1/59 (because of excessive salivation). There was no occurrence of any other of the observed-for events (eg, hypoxia, hypotension, apnea, cyanosis, or nausea).

In the 6- to 7-year-old age group, the mean age was 78.2 ± 4.6 months. The mean weight was 24.7 ± 6.5 kg. There were 38 boys and 11 girls. All 49 children in this age group were classified as ASA class 1. The mean initial dose of propofol was 3.70 ± 1.30 mg/kg (n = 49 children), and the mean of the subsequent bolus doses was 1.40 ± 0.80 mg/kg (n = 9 children). Complete interval data (with the exception of expired carbon dioxide tension) were available for all children for 0–105 minutes, and >93% of children for 106–120 minutes. For time periods longer than 120 minutes complete interval data were present in fewer than half of the children

because of earlier completion of the MRI/MRS procedure. Table 3 displays the interval data for 0–120 minutes for this age group. The range of individual propofol infusion rates was 180–235 µg/kg/min. As above, notable events were recorded for all children regardless of the duration for which complete interval data were available. There was only 1 notable event (Table 2). One MRI/MRS procedure was terminated prematurely because of disconnection of the intravenous tubing through which propofol was being infused. Disconnection occurred while the child was moved into and out of the scanner for head repositioning to permit coregistration with age 3 MRI/MRS. When the child was noted to move while in the scanner, the bed and child were removed immediately from the scanner. On awakening, the child stated “I had a dream.” The child did not appear upset either at the time of awakening or at any other time before leaving the UW Diagnostic Imaging Center with his parents, and no adverse aftereffects were

TABLE 3. Physiological Values in 6- to 7-Year-Old Children

	0–15 min	16–30 min	31–45 min	46–60 min	61–75 min	76–90 min
sPo ₂ (%)	97.1 ± 3.8 N = 49	97.2 ± 3.8 N = 49	97.2 ± 4.0 N = 49	97.1 ± 3.9 N = 49	97.2 ± 4.0 N = 49	97.5 ± 3.9 N = 48
Systolic blood pressure (mm Hg)	104.0 ± 10.3 N = 49	96.4 ± 8.0 N = 49	93.9 ± 8.4 N = 49	93.0 ± 8.2 N = 49	93.1 ± 8.4 N = 49	95.0 ± 9.1 N = 48
Diastolic blood pressure (mm Hg)	46.0 ± 8.2 N = 49	38.1 ± 6.2 N = 49	35.2 ± 5.8 N = 49	34.6 ± 6.1 N = 49	33.9 ± 5.5 N = 49	35.0 ± 5.7 N = 48
Heart rate (beats/min)	90.9 ± 9.4 N = 49	86.7 ± 9.5 N = 49	85.3 ± 8.4 N = 49	85.2 ± 8.9 N = 49	85.0 ± 8.9 N = 49	84.7 ± 8.7 N = 48
Propofol infusion rate (µg/kg/min)	199.3 ± 4.6 N = 49	202.5 ± 8.9 N = 49	203.7 ± 10.6 N = 49	203.5 ± 10.8 N = 49	203.4 ± 10.7 N = 49	202.1 ± 12.5 N = 48
	91–105 min	106–120 min	121–135 min	136–150 min	151–165 min	
sPo ₂ (%)	97.7 ± 3.9 N = 48	98.0 ± 3.9 N = 44	97.8 ± 1.7 N = 35	98.1 ± 1.6 N = 18	98.9 ± 1.0 N = 9	
Systolic blood pressure (mm Hg)	97.6 ± 9.6 N = 48	99.8 ± 10.4 N = 46	102.8 ± 10.6 N = 38	104.1 ± 10.3 N = 22	113.5 ± 7.5 N = 11	
Diastolic blood pressure (mm Hg)	37.6 ± 6.3 N = 48	40.5 ± 6.9 N = 46	41.9 ± 8.1 N = 38	44.1 ± 7.0 N = 22	48.7 ± 6.4 N = 11	
Heart rate (beats/min)	85.1 ± 9.1 N = 48	85.7 ± 9.5 N = 46	86.9 ± 8.9 N = 37	88.7 ± 9.7 N = 22	93.4 ± 11.6 N = 11	
Propofol infusion rate (µg/kg/min)	202.3 ± 12.8 N = 48	204.1 ± 10.5 N = 46	203.6 ± 10.9 N = 38	206.7 ± 14.5 N = 22	210.0 ± 16.7 N = 11	

sPo₂, oxyhemoglobin saturation.

reported. In this 6- to 7-year-old age group there was no occurrence of any of the other observed-for events (eg, hypoxia, hypotension, obstruction, apnea, cyanosis, nausea).

In both age groups MRI/MRS data from the study groups were of excellent quality, with only 2/108 studies (2%) excluded because of technical limitations. In contrast, a significantly higher proportion of MRI/MRS studies in typically developing children (no propofol sedation) at 3–4 years of age (~70%) and at 6–7 years of age (~50%) either failed, resulted in only partial data acquisition (MRI or MRS), or data were not of satisfactory quality. Studies in these control children were attempted late at night (10:00 PM to 2:00 AM) without the use of propofol sedation. Excluding children with clinically significant brain structural abnormalities or questionable clinical depression, 38 of 55 (69%) of children studied at 3–4 years of age returned at 6–7 years of age for longitudinal follow-up. Brain tissue lactate was not increased in either gray or white matter either with or without the use of propofol sedation.³⁷

All families in the study groups left the recovery area within 60 minutes after conclusion of MRI/MRS. During a follow-up telephone call at 24 hours, 1 parent expressed a concern that her child had a low-grade fever, which later was concluded to be unrelated to the MRI/MRS procedure. A high proportion of parents stated their intention for their child to return for subsequent MRI/MRS at 9–10 years of age.

Aggregate data analysis (this study and previous reports^{2–32}) indicated that the incidence of reports of 1 or more major adverse events was 67% among studies in which an invasive or painful procedure was performed, significantly increased compared with 25% among studies in which procedures were not invasive or painful (Table 4). The incidence was 80% among studies in which fewer than 99% of patients were

ASA status 1, significantly increased compared with 0% among studies in which more than 99% of patients were ASA status 1. The incidence was 77% among studies in which a non-anesthesiologist physician provided sedation, significantly increased compared with 17% among studies in which an anesthesiologist provided sedation. The incidence was 100% among studies in which supplemental oxygen was not used routinely, significantly increased compared with 21% among studies in which supplemental oxygen was used (see Discussion for details).

DISCUSSION

The principal findings of our study are that propofol sedation in conjunction with careful physiological monitoring of children during research MRI/MRS is both safe and effective. Two findings attest to the safety of our procedure. First, the few events that occurred were not events associated with high risk such as hypoxia, apnea, significant hypotension, ischemia/cyanosis, and severe cardiac dysrhythmia. Second is the low incidence of minor events, ie, 2/59 partial airway obstructions and 1/59 bradycardia, in 3- to 4-year-old children and 0/49 in 6- to 7-year-old children. Additionally, during propofol sedation no increase in brain tissue lactate was detected by our MRS chemical quantification, a technique of proven sensitivity to detect increased gray matter lactate in medication-free patients with bipolar disorder.^{37,41}

Similarly, 2 findings attest to the effectiveness of our procedure. First, there was a substantial success rate for acquisition of high-quality imaging/spectroscopic imaging data from this difficult-to-study clinical population. Second, parents generally were satisfied with their child's MRI/MRS experience, there was a high rate of return for MRI/MRS at 6–7 years following the studies at 3–4 years, and a high proportion of parents stated their intention for their child to return for subsequent MRI/MRS at age 9–10 years following the studies at age 6–7 years.

Minor Events, Satisfaction, and Imaging Quality

Table 5 compares the outcome measures in our study to those of previous reports of pediatric sedation. In our study, the incidence of events not associated with high risk (termed hereafter “minor events”) was similar to or less than that in previous reports. Our incidence of partial airway obstruction (<2%) was comparable to that reported in most previous studies (0%–4%)^{5–8,15,17–20,24} and substantially less than that reported in 2 other studies (12%–17%).^{13,22} Bradycardia in our study (<1%) was similar to that in most previous reports (<1%)^{5,6,16,23,32} and less than in 1 other report (6%).⁷ Our incidence of other minor dysrhythmias (0%) was comparable to those in previous reports (<1%).^{5–7,16,20,26,31} Nausea and/or vomiting in our study (0%) was similar to those in most previous reports (0%–2.5%)^{5,6,8,9,14,16,19,20,23,26,31} and substantially less than in 1 other study (32%).²⁴ The incidence of agitation (0%) was comparable to those in most previous reports (0%–1.2%)^{18,23,26,31} and less than in 3 other studies (4%–8%).^{14,19,24} Other minor events reported by others include

TABLE 4. High Incidence of Major Events

Factor	Proportion	Fisher Exact Test
Proportion of reports with high incidence of hypoxia, apnea, or hypotension related to:		
Procedure		$P < 0.05$
Invasive or painful	10 of 15 reports	
Not invasive or painful	1 of 4 reports	
ASA status		$P < 0.05$
<99% of patients ASA 1	8 of 10 reports	
>99% of patients ASA 1	0 of 1 report	
Sedating physician		$P < 0.05$
Nonanesthesiologist	10 of 13 reports	
Anesthesiologist	1 of 6 reports	
Sedation drug		NS
Other drug(s) plus propofol	8 of 13 reports	
Propofol alone	5 of 13 reports	
Proportion of reports with high incidence of hypoxia only related to:		
Supplemental oxygen		$P < 0.05$
Not used	2 of 2 reports	
Used	3 of 14 reports	

pain on drug injection (5%) but not recall of that pain, and recall of the procedure for which sedation was used (16%).^{16,24} Our high rate of child/parent satisfaction and success rate of imaging are similar to or better than those in previous reports.^{8,9,11,16,21,32}

Major Events

Our incidence of either (1) events associated with high risk (termed hereafter “major events”) such as hypoxia, apnea,

significant hypotension, poor perfusion/cyanosis, and severe cardiac dysrhythmias, or (2) major negative outcome was similar to or less than that in previous reports. Our incidence of major events was 0%, whereas in previous studies the incidence range for hypoxia was 0%–30%,^{2–9,12,14,16,17,19–24,26,30–32} for apnea was 0%–20%,^{2,5–9,13,14,16,17,20–24,26} for hypotension was 0%–68%,^{2,5–9,12–14,17,20,22–24,26,30,32} for poor perfusion/cyanosis was 0%,^{2,5–7,16,22,23} and for severe cardiac dysrhythmias was 0%.^{5–7,16,26} Our incidence of major negative outcome (0%) was comparable to that in previous studies (0%).^{2–9,11–14,16–31}

TABLE 5. Outcome Measures

Reference	Date	Hypoxia	Hypercapnia	Partial Airway Obstruction	Apnea/Complete Airway Obstruction	Hypotension
Amundsen et al	Current	0	0	2/59 (3.4%)	0	0
Yildzdas et al ²	2004	3/25 (12%)	13/25 (52%)	0	0	0
Wengrower et al ³	2004	21/296 (7.1%) (90% in ASAIII)			0	0
Hosey et al ⁴	2004	0 (1/32 < 92%)				
Wheeler et al ⁵	2003	0 (3/91 < 92%)		0	0	3/91 (3.3%)
Guenther et al ⁶	2003	20/291 (6.9%)		4%	3/291 (1%)	50/291 (17.2%)
Bassett et al ⁷	2003	5%		11/392 (2.8%)	3/392 (0.8%)	35/392 (8.9%)
Barbi et al ⁸	2003	52/432 (12%) without O ₂ ; 12/626 (1.9%) with O ₂		10/1059 (0.9%)	5/1059 (0.5%)	137/1059 (12.9%)
Hasan et al ⁹	2003	0			0	0
Usher et al ¹⁰	2003					
Klein et al ¹¹	2003					1/40
Punj et al ¹²	2002	0				0
Vardi et al ¹³	2002			12/58 (20.7%)	10/58 (17.2%)	6/58 (10.3%)
Kaddu et al ¹⁴	2002	6/25 (25%)			20%	24% had decrease >20 mm Hg
Seigler et al ¹⁵	2001			1/261 (0.38%) (treated with intubation)		
Skokan et al ¹⁶	2001	30% without O ₂ ; 0% with O ₂		0	0	0
Dial et al ¹⁷	2001 propofol only Multiple/various agents*	0 16/301		0 9/301 (2.99%)	0 8/301 (2.67%)	0 19/301 (6.31%)
Koh et al ¹⁸	2001			22/720 (3.06%)		
Jayabose et al ¹⁹	2001	6/52 (11.54%)		1/52 (1.92%)		
Seiler et al ²⁰	2001	25/837 (2.99%)		0	12/837 (1.43%)	0
Elitsur, et al ²¹	2000	0			0	
Hertzog, et al ²²	2000	2/50 (4%)		6/50 (12%)	1/50 (2%)	68%
Masters, et al ²³	2000	0			0	0
Havel, et al ²⁴	1999	5/43 (11.63%)		0	0	0
Reber, et al ²⁵	1999					
Bauman, et al ²⁶	1999	0		0	1/X#	0
Fortney, et al ²⁷	1999					
Souweidane et al ²⁸	1999					
Barst, et al ²⁹	1995					
Merola, et al ³⁰	1995	0				0
McDowall, et al ³¹	1995	96/603 (15.92%)				
Bloomfield, et al ³²	1993	3/31 (9.68%)				12/31 (38.7%)

(continued on next page)

TABLE 5. (continued) Outcome Measures

Reference	Average Decrease of Systolic Blood Pressure	Bradycardia	Dysrhythmia	Poor Perfusion/ Cyanosis	Agitation	Nausea and/or Vomiting	Negative Outcome	Success/ Satisfaction
Amundsen et al		1/59 (1.7%)	0	0	0	0	0	Success 58/59
		0	0	0	0	0	0	48/49
Yildzdas et al ²	0	0	0	0			0	
Wengrower et al ³							0	
Hosey et al ⁴							0	
Wheeler et al ⁵		0	0	0		0	0	
Guenther et al ⁶	Median 22 mm Hg	1/291 (0.3%)	0	0		1/291 (0.3%)		
Bassett et al ⁷	Median 10%	23/392 (5.9%)	0	0			0	
Barbi et al ⁸	Mean 16 mm Hg	0			4/1059 (0.4%)	3/1059 (0.3%)	0	Satisfaction 95.8%–100%; parental concern 5%–8.1%
Hasan et al ⁹	Mean 12 mm Hg				0	0	0 (2% myoclonus)	Satisfaction 100%; parental concern 0%
Usher et al ¹⁰								
Klein et al ¹¹	19 ± 10% (bolus) 26 ± 12% (infusion)			0			0 (1/40 recall)	Patient/ parent satisfaction 1 on a 1–3 scale; operator satisfaction 1.3 ± 0.5 on a 1–5 scale
Punj et al ¹²		0					0	
Vardi et al ¹³							0	
Kaddu et al ¹⁴					8%	0	0	
Seigler et al ¹⁵							0	
Skokan et al ¹⁶	Mean 18 mm Hg	0 (Mean decrease HR 16 beats/min)	0	0	0	1/40 (2.5%)	0 (5% pain on propofol injection)	Patient satisfaction 97.3%–100%; parent satisfaction 94.6%–94.7%; physician satisfaction 92.5%
Dial et al ¹⁷							0	
Koh et al ¹⁸		1/301 (0.33%)				*31/720(4%) (postop pain or nausea/ vomiting or decrease respirations)	0	
Jayabose et al ¹⁹					2/52 (3.85%)	1/52 (1.92%)	0	
Seiler et al ²⁰			13/837 (1.55%) increase HR only			6/837 (0.72%)	0	
Elitsur, et al ²¹							0	Satisfaction 90%–99%
Hertzog, et al ²²	Mean 25 ± 10%			0			0	
Masters, et al ²³	14%	0		0	0	0	0	
Havel, et al ²⁴	2%–18%				2/43 (4.65%)	32%	0 (16% recall)	
Reber, et al ²⁵							0	

TABLE 5. (continued) Outcome Measures

Reference	Average Decrease of Systolic Blood Pressure	Bradycardia	Dysrhythmia	Poor Perfusion/Cyanosis	Agitation	Nausea and/or Vomiting	Negative Outcome	Success/Satisfaction
Bauman, et al ²⁶			0		0	0	0	
Fortney, et al ²⁷							0	
Souweidane et al ²⁸							0	
Barst, et al ²⁹							0	
Merola, et al ³⁰							0	
McDowall, et al ³¹			3/603 (0.5%) increase HR only		7/603 (1.16%)	3/603 (0.5%)	0	
Bloomfield, et al ³²	37.5% or 29 mm Hg	Mean decrease HR 21 ± 15%					0	Satisfaction 100%

Hypoxia, oxyhemoglobin saturation <90%; hypercapnia, expired CO₂ > 50 mm Hg; partial airway obstruction, snoring/obstruction easily relieved by jaw lift/head repositioning; apnea, no breath for >10 seconds; hypotension, decrease of >30% systolic blood pressure from baseline or to below 5th percentile for age; bradycardia, heart rate <80 beats/min in 3- to 4-year-old children and <75 beats/min in 6- to 7-year-old children; dysrhythmia, irregular, fast or slow pulse rate accompanied by hypotension; poor perfusion, decreased skin perfusion; cyanosis, visible skin discoloration.

Dial et al: All sedation types combined (ie, chloral hydrate, midazolam, ketamine, propofol, barbiturates, fentanyl in various combinations), all adverse events combined in 301 patients; 0% ASA I, 23% ASA II, 17% ASA III, 100% ASA IV (1 patient).

#Denominator not stated; patient having procedure following earlier procedure for which sedation was used.

Factors Increasing the Incidence of Major Events

Implicit in Table 5 are certain patient care factors such as monitoring oxyhemoglobin saturation and blood pressure, observance of respiration, pulse regularity and rate, skin perfusion, etc. Table 6 displays additional patient care variables and characteristics of our study and previous reports of pediatric sedation. Patient care factors displayed in Table 6 include patient age and weight, physical status (usually assessed using the “grading” format approved by the ASA), initial “loading” dose and subsequent infusion or bolus doses of propofol, administration of other medications along with propofol, use of supplemental oxygen, and monitoring of expired carbon dioxide tension.³⁵ We correlated these patient care factors and also the procedure for which sedation was given with the outcome data from Table 5 in an effort to determine which factors may contribute to increased incidence of major events. Of the 6 events we defined as major (see above), hypoxia, apnea, and hypotension occurred in 1 or more of the previous reports on pediatric sedation, but poor perfusion/cyanosis, severe cardiac dysrhythmia, and negative outcome did not. Thus, our analysis included only the reports in which information was available for the factor of interest (ie, ASA status, procedure) and for at least 2 of the 3 major outcome measures (hypoxia, apnea, or hypotension). A report was scored “positive for major event” if the incidence of at least 1 major event was notably higher than the average incidence for that event among all previous studies (ie, the incidence of hypoxia, apnea, or hypotension was greater than or equal to 5%).

The above analysis indicated that a high incidence of 1 or more major events was associated with the procedure for which sedation was provided, ASA status of the patients, and whether or not the physician administering sedation was an anesthesiologist, but not with administration of premedication

or addition of other medications along with propofol (Table 4). In the 1 study that reported incidence of major events as a function of ASA status, major events occurred in 0% of ASA 1 patients, 23% of ASA 2 patients, and 17% of ASA 3 patients.¹⁷ The analysis performed to generate Table 4 also indicated that failure to provide supplemental oxygen was associated with hypoxia. In the studies that used supplemental oxygen in some patients and not in others and reported the incidence of hypoxia as a function of supplemental oxygen use, hypoxia occurred in 12% of patients without supplemental oxygen and in 1.9% of patients with supplemental oxygen in 1 study, and in 30% of patients overall, but in none of the patients with supplemental oxygen in the second study.^{8,16} There was insufficient information about monitoring of expired carbon dioxide tension and incidence of apnea or administration of intravenous fluid and incidence of hypotension to draw any conclusions about those factors.

Comparison Between Propofol and Other Sedation Techniques

A number of previous studies were designed to compare children sedated with propofol to children sedated with other techniques. Reported benefits of propofol were higher satisfaction scores, lower incidence of hallucinations, less blood pressure decrease, less postprocedure narcotic use, and shorter time to awakening, recovery, and discharge.^{13,14,20,24,32} Reported disadvantages of propofol were increased mean end-tidal CO₂, greater need for airway intervention, longer time to awaken, and transient decrease of oxyhemoglobin saturation and pulse rate.^{2,13,14,20,32}

A number of other previous studies provide data on groups of children sedated with propofol and with other techniques, although the studies were not prospectively designed to make comparisons between the groups. Benefits of

propofol included lower incidences of respiratory and cardiovascular adverse events, vomiting, tachycardia, agitation, and myoclonus, and a lower percentage of patients with 1 or more complications.^{17,20,30,31} One study reported a higher

incidence of oxyhemoglobin saturation <94% with propofol that was “easily managed with supplemental oxygen.”³¹ Multiple studies reported no difference in efficacy or adverse effects between propofol and numerous other drugs (sedatives,

TABLE 6. Patient Care Variables and Characteristics

Reference	Date	Age	Number of Children	Number of Procedures	ASA Status	Weight (kg) (mean)	Anesthesiologist Was the Care Provider, Y/N
Amundsen et al	Current	4.0 ± 0.4 yr	59	59	I, 58; II, I	18.6 ± 4.2	Y
		6.5 ± 0.4 yr	49	49	I, 49	24.7 ± 6.5	Y
Yildzdas et al ²	2004	8.3 ± 3.7 yr	126	126	?I or II		N? pediatric intensivist
Wengrower et al ³	2004	4.5 yr	296	296	I, 15%; II, 57%; III, 28%		Y
Hosey et al ⁴	2004	12.8 yr	34		I	54.6	N? dentist ?none
Wheeler et al ⁵	2003	9.3 yr	91	110			N, pediatric intensivist
Guenther et al ⁶	2003	6 yr	87	291	I, 4%; II, 6%; III, 90%		N, emergency physician
Bassett et al ⁷	2003	8 yr		393	I, 379; II, 13		N, emergency physician
Barbi et al ⁸	2003	1–21 yr		1059	I or II		N, pediatric fellow (anesthesiologist back-up)
Hasan et al ⁹	2003	4.2 ± 3.1 yr	115	115	I, 69%; II, 31%		N, pediatric intensivist
Usher et al ¹⁰	2003						Y
Klein et al ¹¹	2003	7 ± 5.4 yr (bolus)					
		8.1 ± 5.6 yr (infusion)	22	40	I or II		N, pediatric intensivist
Punj et al ¹²	2002						
Vardi et al ¹³	2002	7.5 ± 5.7 yr	98	105 (58 propofol/lidocaine; 47, ketamine/midazolam/fentanyl)	I, 7; II, 96; III, 2		N, pediatric intensivist
Kaddu et al ¹⁴	2002	8.3 ± 3.7 yr (propofol)	25	25			
		8.0 ± 5.6 yr (isoflurane)	25	25			Y
Seigler et al ¹⁵	2001	1 mo–22 yr		261-propofol 144-ketamine			N, pediatric intensivist
Skokan et al ¹⁶	2001	7.4 yr	40	40	I or II		N, emergency physician
Dial et al ¹⁷	2001	7±6 yr	214	301	I, 33 (11%); II, 204 (68%); III, 63 (21%); IV, I		N, critical care physician
Koh et al ¹⁸	2001	9.7 yr	720	720	I-II 93% III 6%		Y
Jayabose et al ¹⁹	2001		52	335			Y
Seiler et al ²⁰	2001	3.8 yr		837	?II or III		Y
Elitsur et al ²¹	2000	>2 yr	104	107			Y
Hertzog et al ²²	2000	7.5±4.3 yr	28	50	?II or III		N-pediatric intensivist
Masters et al ²³	2000	12.5 yr	24	24			Y
Havel et al ²⁴	1999	2–18 yr	43	43	I, 36; II, 7		N, emergency physician
Reber et al ²⁵	1999	5 ± 3 yr	10	10		21 ± 12	Y
Bauman et al ²⁶	1999	6.6 yr	64	64			Y
Fortney et al ²⁷	1999	2.6 ± 1.8 yr	29	29	?II or III		Y
Souweidane et al ²⁸	1999	2.75 yr	8	8	II or III		Y
Barst et al ²⁹	1995						
Merola et al ³⁰	1995		324	324			
McDowall et al ³¹	1995	7.8 ± 0.2 yr	603	603		28.3 ± 0.7	Y
Bloomfield et al ³²	1993	5 yr	31	31	I, 4	20	Y, first 10 patients
					II or III, 27		N, radiologist after first 10 patients

TABLE 6. (continued) Patient Care Variables and Characteristics

Reference	Propofol Initial Bolus (mg/kg)	Propofol Infusion (µg/kg/min)	Propofol Additional Bolus (mg/kg)	Propofol Total Dose (mg/kg)	Other Meds	Supplemental O ₂	ETCO ₂ Monitor Y/N
Amundsen et al	3.07 ± 1.16	200 ± 14	0.90 ± 0.28		None	FM	Y
	3.7 ± 1.3	203 ± 10	1.4 ± 0.8			FM	
Yildzdas et al ²	2	None	None		None; Other protocols -a	NC	Y-nasal
Wengrower et al ³	0.5–1.0	50	None		None or midazolam 0.1–0.2 mg/kg Other protocols-b	FM, intubation	Y
Hosey et al ⁴				2.5 (0.2–5.4)	?None		N
Wheeler et al ⁵	2.41	179.3		4.23	Lidocaine 1% Fentanyl 1 µg/kg	BBM, NC	N
Guenther et al ⁶	1		0.5	3.9	Fentanyl 1–2 µg/kg (max 50 µg)#	BBM	N
Bassett et al ⁷	1 (max 40 mg)		0.5 (max 20 mg)	2.9	Morphine 0.1 mg/kg* (44/393 = 11%) Fentanyl 1–2 µg/kg* (282/393 = 72%)	BBM	N
Barbi et al ⁸	1.0–2.0	100–150	0.5–1	3.8 ± 1.2 to 7.0 ± 2.1	Atropine 0.01 mg/kg	CPAP, NC	N
Hasan et al ⁹	1.0–3.0	17–33	1	4.3 ± 1.7	Lidocaine 10 mg	NC	Y
Usher et al ¹⁰	3.7 (2–6)	165 (100–250)				FM, NC	Y
Klein et al ¹¹	1.5	100 (increase by 20% if bolus)	0.5	5.7 + 2.4 (bolus)		BBM	N
	1.8			8.0 ± 3.8 (infusion)			
Punj et al ¹²	2.5				Lidocaine 0.1 mg/kg Other protocols-c	BBM, FM (O ₂ only if O ₂ SAT fall to 94–95%)	N
Vardi et al ¹³	2.5 (children) 3.0 (infants)	200	1		Lidocaine 1 mg Other protocols-d	BBM, FM	N
Kaddu et al ¹⁴		300, titrate to 500 prn			O ₂ /N ₂ O 2%–4% Halothane for IV start Other protocols-e	NC intubation	
Seigler et al ¹⁵					Midazolam, atropine, or glycopyrrolate Other protocols-f	FM	
Skokan et al ¹⁶	1 (max 40 mg)		0.5 (max 20 mg)	3.3	Morphine 0.1 mg/kg (max 5 mg) or fentanyl 1 µg/kg (max 100 µg)	Y	N
Dial et al ¹⁷	0.5–2.0	50–133	0.2				N
Koh et al ¹⁸				5.9–10.6	Midazolam, fentanyl, alfentanil	BBM	
Jayabose et al ¹⁹					Fentanyl, midazolam, fentanyl and midazolam		
Seiler et al ²⁰				4.8			
Elitsur et al ²¹				5.4 ± 2.7 3.1 ± 1.3 5.0 ± 3.0	19, none; 32, midazolam and/or fentanyl; 56, midazolam	Y	
Hertzog et al ²²	2.0 ± 0.8			6.6 ± 2.3, 0 to 7.9 ± 2.4	Lidocaine 10 mg	BBM	
Masters et al ²³		50–55	1.05		17-none 7-O ₂ /N ₂ O/fentanyl	FM,NC	

(continued on next page)

TABLE 6. (continued) Patient Care Variables and Characteristics

Reference	Propofol Initial Bolus (mg/kg)	Propofol Infusion ($\mu\text{g}/\text{kg}/\text{min}$)	Propofol Additional Bolus (mg/kg)	Propofol Total Dose (mg/kg)	Other Meds	Supplemental O ₂	ETCO ₂ Monitor Y/N
Havel et al ²⁴	1	67–117	1		Morphine 0.05–0.1 mg/kg (max 5 mg) (mean total 0.24 mg/kg); lidocaine 0.5 mg/kg	O ₂ only if O ₂ SAT < 93%	
Reber et al ²⁵	3	133–167	1			NC	
Bauman et al ²⁶	3.4	150			Fentanyl 1.1 $\mu\text{g}/\text{kg}$		
	1.5–2.0				Fentanyl 1.0 $\mu\text{g}/\text{kg}$		
Fortney et al ²⁷						Y	Y
Souweidane et al ²⁸		50–225				NC	
Barst et al ²⁹							
Merola et al ³⁰							
McDowall et al ³¹	3	None	PRN	3.5 \pm 2.41	Fentanyl 1 $\mu\text{g}/\text{kg}$ or alfentanil 10 $\mu\text{g}/\text{kg}$	FM,NC PRN	
Bloomfield et al ³²	2.7	100–167	1		Glycopyrrolate 0.05/12 kg^{-1} Lidocaine 10–20 mg	NC	

Age: x = mean or median; x \pm x = mean \pm variance; x–x = range; mo, months; yr, years.

Weight: mean or mean \pm SD.

Propofol dose: x = total dose, (x–x) = range, x \pm x = total dose \pm SD.

Supplemental O₂: FM, face mask; NC, nasal cannula; BBM, blow-by mask.

CPAP, continuous positive airway pressure.

O₂SAT: oxyhemoglobin saturation.

?: Data not stated in report but inferred from other information in report.

Blank: data not stated and not able to be inferred.

#Guenther et al: premed; 5/291 different preop narcotic than fentanyl, 3/291 no narcotic premed.

*Bassett et al: mean fentanyl dose 1.2 $\mu\text{g}/\text{kg}$, mean morphine dose 0.08 mg/kg.

Other protocols: a, ketamine 1 mg/kg; midazolam 0.15 mg/kg; ketamine 1 mg/kg + midazolam 0.1 mg/kg; midazolam 0.1 mg/kg + fentanyl 2 $\mu\text{g}/\text{kg}$.

b, O₂/N₂O/halothane. c, ketamine 10 mg/kg. d, midazolam 0.1 mg/kg + ketamine 2 mg/kg + fentanyl 2 $\mu\text{g}/\text{kg}$. e, O₂/isoflurane 1.5–2.0% + mivacurium 0.2 mg/kg. f, ketamine.

opioids, anxiolytics, dissociatives, and etc.) alone or in combination.^{18,19,21,26,27,29}

Both of the above-mentioned groups of studies (those designed with the intent to compare propofol to 1 or more other sedation techniques and those making retrospective comparisons between propofol and other techniques) provide additional support for the safety of propofol sedation for children.

SUMMARY

We designed a protocol for propofol sedation and monitoring of children participating in an ongoing longitudinal imaging research project investigating brain developmental processes associated with ASD and IDD. In our study, propofol sedation for research MRI/MRS in children was highly effective and resulted in few notable events and no major events (eg, hypoxia, apnea, hypotension, poor perfusion/cyanosis, major cardiac dysrhythmia, or negative outcome). Our results were similar to or better than those previously reported (31 recent studies) with clinical sedation of children for procedures that were noninvasive or invasive and diagnostic or therapeutic.^{2–32} Analysis of the aggregate of our data and previous reports indicates that factors associated with major events include (1) invasive or painful procedures, (2) ASA status higher than class 1, (3) administration of sedation by a nonanesthesiologist,

and (4) failure to provide supplemental oxygen. We conclude that propofol sedation for research MRI/MRS is safe and effective providing children of appropriate ASA status are selected, supplemental oxygen is delivered, and sedation and monitoring are done by an experienced anesthesiologist.

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APPENDIX

A total of 108 MRI/MRS studies using propofol sedation were performed in the study group of affected children, which included 45 children with ASD and 14 children with IDD at ages 3–4 years old and 35 with ASD and 14 with IDD at ages 6–7 years old. The diagnosis ASD included children with autism disorder (AD) and pervasive developmental disorder, not otherwise specified (PDD-NOS). Of the 108 MRI/MRS studies in this group, 38 children (29 with ASD and 9 with IDD) were studied at both time points. Study children were sedated with propofol, and physiological values were monitored and recorded (see below). A control group of 26 children with typical development also was studied. This comparison group was needed because there are no previous reports providing data on rates of success/failure, partial data acquisition, or satisfactory quality of data for MRI/MRS studies of ~2 hours duration done for research purposes. These children were either not sedated (N = 18) or given diphenhydramine 25 mg PO (N = 8) for MRI/MRS studies, and physiological values were not monitored. For this study we used propofol as an alternative to IV Nembutal or oral chloral

hydrate “bolus sedation” because we anticipated that propofol would be better titrated to achieve successful exams with the most positive experience for the children and their parents. Use of propofol was made possible by the availability of an anesthesiologist for administration and monitoring. In contrast, for control studies of healthy, typically developing, age-matched children, propofol sedation was not a viable option because of ethical considerations and pragmatic factors of parental acceptability. In performing studies in nonsedated, control children at ages 3–4 years old and 6–7 years old, we attempted late night studies (eg, beginning at 10:00 PM and ending as late as 1:00 AM). Failures with this approach led us to schedule the studies progressively later at night (eg, beginning at 2:00 AM). Despite attempting studies progressively later at night, there was a high failure rate (approximately 70% for children at ages 3–4 years old and 50% for children at ages 6–7 years old) at keeping children in the scanner or acquiring completed MRI/MRS studies not invalidated by movement artifact. Because of the high failure rate or partial data acquisition in late

night studies of children at ages 3–4 years old, MRI studies were augmented by structural data acquisition from the National Institutes of Health.^{36,37}

The diagnostic workup for these children has been detailed elsewhere.^{36,37} Participants were recruited from local parent advocacy groups, public schools, the Department of Developmental Disabilities, clinics, hospitals, and the University of Washington Infant and Child Subject Pool. Written parental/guardian, informed consent, approved by the University of Washington Internal Review Board, was obtained for each child. Children having identifiable genetic abnormalities (eg, Fragile X syndrome, Norrie syndrome, neurofibromatosis, tuberous sclerosis, phenylketonuria, Down syndrome), cerebral vascular disease, severe sensory or motor impairments (deaf/blind), significant pulmonary disease, unstable cardiovascular status, major physical abnormalities, documented pre- or postnatal head trauma, metal implants such as prostheses, and/or regularly taking psychoactive medication were excluded from participation.