CME An Assessment of the Effects of General Anesthetics on Developing Brain Structure and Neurocognitive Function

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BACKGROUND: Neuronal cell death after general anesthesia has recently been documented in several immature animal models. Worldwide, volatile anesthetics are used in millions of young children every year during surgical procedures and imaging studies. The possibility of anesthesia-induced neurotoxicity during an uneventful anesthetic in neonates or infants has led to serious questions about the safety of pediatric anesthesia. However, the applicability of animal data to clinical anesthesia practice remains uncertain. In the present review, we assess the evidence for the effects of commonly used anesthetics on neuronal structure and neurocognitive function in newborn humans and animals.

METHODS: Medical databases, including Medline, Cinahl, and Pubmed, abstract listings of the American Society of Anesthesiologists, International Anesthesia Research Society, Society for Pediatric Anesthesia, and Society for Neuroscience Annual Meetings, and personal files were queried regarding anesthesia-induced neurotoxicity.

RESULTS: A growing number of studies in immature animal models demonstrate degenerative effects of several anesthetics on neuronal structure. A few studies reveal cognitive impairment in adult animals after neonatal anesthesia. There are no prospective studies evaluating neurocognitive function in children after neonatal exposure to anesthetics. However, several retrospective reviews demonstrate temporary neurological sequelae after prolonged anesthetic exposure in young children and larger studies identify long-term neurodevelopmental impairment after neonatal surgery and anesthesia.

CONCLUSIONS: The evidence for anesthesia-induced neurodegeneration in animal models is compelling. Although this phenomenon has not been prospectively studied in young children, anecdotal data point toward the possibility for neurological impairment after surgery and anesthesia early in life. Given the serious implications for public health, further investigations of this phenomenon are imperative, both in laboratory animals and in young children.

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Primum non nocere, this central maxim of medicine, is even more paramount for pediatric medicine, which treats the most vulnerable of patient populations. Pediatric anesthesia, which plays a part in the rapid advancement of anesthesiology, prides itself in having rendered surgical procedures now routine and safe in the smallest of patients, which were unthinkable 20 or 30 yr ago. Although the risk of anesthetic complications due to physiological differences remains higher in neonates and infants compared with adults,[1] millions of children every year undergo seemingly safe general anesthetics for surgical procedures and imaging studies. Moreover, the appreciation for the infants' stress response during surgery and the identification of the deleterious effects of inadequate anesthesia and analgesia during painful procedures in the developing brain have resulted in the current use of balanced anesthesia techniques.[2] However, recent data in laboratory animals have raised significant concerns among anesthesiologists, neuroscientists, parents, the lay press, and electronic media regarding the safety of general anesthetics in infancy and their effects on normal brain development.[3–8] Although the neurodegenerative effects of ketamine in animal models have recently been reviewed in this journal,[9] the current article aims to provide an overview of the available evidence of degenerative or toxic effects of all commonly used general anesthetics in the developing brain, animal or human, and to put the available laboratory data into clinical perspective. We thereby intend to give a balanced view of this currently predominant controversy in pediatric anesthesiology.

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Growth and development of the mammalian central nervous system (CNS) involve complex cellular processes such as neurogenesis, differentiation into specialized cell subspecies, migration of cells to their final destination in the CNS, synaptogenesis with connection formation, and axonal myelination. These processes vary significantly in duration and timing, relative to gestational age, among different mammalian species, in accordance with their life expectancy.[10] In humans, synaptogenesis starts during the third trimester of gestation and rapid brain growth continues for up to 2 to 3 yr after birth.[11] In small rodents, such as mice and rats, the brain is relatively immature at birth and matures very rapidly during the first 2 wk of life.[12] The brain developmental stage of the 7-day-old postnatal mouse or rat has historically been considered equivalent to the human neonate at approximately 32–36-wk gestation.[10,13]

During normal CNS development, neurons are produced in excess and the elimination of supernumerary neurons is critical for achieving normal brain morphology, brain size, and viability of the organism. Importantly, as part of normal brain development, as much as 50%–70% of neurons and progenitor cells undergo physiological cell death and elimination by an inherent cell death program, termed apoptosis, which is centered around the caspase enzyme family.[14–19] Disruption of this massive, physiological cell death mechanism leads to intrauterine malformation of the brain and premature death of the embryo.[20]

The diverse group of clinically used general anesthetics spans from IV anesthetics, such as benzodiazepines, barbiturates, ketamine, propofol, and etomidate, to inhaled anesthetics, such as halothane, isoflurane, sevoflurane, desflurane, nitrous oxide, and xenon. Although these compounds are chemically very dissimilar, strikingly, their proposed mechanism of action to inhibit neuronal activity is very similar, entailing, to varying degrees, alterations of synaptic transmission involving γ–aminobutyrate (GABA) and/or *N*-methyl-D-aspartate (NMDA) receptors.[21] Because GABA- and NMDA-mediated neuronal activity is essential for mammalian brain development, exposure to general anesthetics could potentially interfere with normal brain maturation.[22,23]

Supporting this possibility, several laboratory studies in neonatal animal models, such as the 7-day-old mouse and rat, demonstrate that administration of anesthetic drugs was associated with an increase in the normal apoptotic neuronal degeneration. This phenomenon has sparked controversy about the implications for pediatric anesthesia.[4,6,7,24–27] It has repeatedly been argued that the laboratory findings in 7-day-old rodents provide evidence for human susceptibility to anesthesia-induced neurotoxicity from the third trimester of pregnancy up to the second year of life.[4,25]

Given the major impact of the possibility of anesthesia-induced neurotoxicity on public health, it appears appropriate to examine the current clinical and preclinical evidence for the effects of various injectable and volatile anesthetics on neuronal structure in the developing brain as well as on subsequent neurocognitive function.

METHODS

Medline (1996–2007), Cinahl (1982–2007), and PubMed searches were performed in June 2007 with the following keywords: brain (newborn or infant or child or neonate or neonatal or animals, newborn) and (neurodegeneration or apoptosis or toxicity or neurocognitive impairment or developmental impairment or developmental disabilities, or learning disorders) and (isoflurane or desflurane or sevoflurane or propofol or etomidate or ketamine or lorazepam or diazepam or midazolam or pentobarbital or phenobarbital or anesthesia, IV or anesthesia, inhalation or anesthesia). In addition, citations in the reference lists of relevant articles, abstracts presented at the 2004–2006 American Society of Anesthesiologists (ASA), 2004–2007 International Anesthesia Research Society (IARS), 2004–2006 Society for Pediatric Anesthesia (SPA), and 2004–2007 Society for Neuroscience (SfN) Annual Meetings as well as personal files were reviewed.

RESULTS

The literature search strategy identified 42 articles. Inspection of their abstracts isolated 17 articles as being relevant to the topic. The remaining articles originated from the reference lists of the originally identified articles, our personal files, and from abstract searches of the American Society of Anesthesiologists, International Anesthesia Research Society, Society for Pediatric Anesthesia, and SfN abstract databases.

No studies were identified describing structural brain abnormalities in children after anesthesia. However, a multitude of studies demonstrate behavioral and neurocognitive abnormalities after surgical anesthesia. Some manuscripts specified the anesthetic regimen (Table 1), whereas others did not detail the particular anesthetics used during surgery (Table 2). Animal studies investigating anesthesia-induced brain structural or behavioral abnormalities are summarized in Table 3.

Postoperative Behavioral Abnormalities

It has long been known that surgery and anesthesia in young children can lead to prolonged behavioral abnormalities.[28–38] Reported behavioral abnormalities, such as attention seeking, crying, temper tantrums, sleep disturbance, and anxiety occur in up to 50% of children early after anesthesia, and decrease significantly during the first postoperative month. These symptoms have repeatedly been associated with younger patient age, severity of postoperative pain, and lack of sedation during anesthesia induction.[28,31,33,36,38] Although the phenomenon's exact

Table 1. Clinical Research Reports on the Effects of Anesthetic Exposure During Early Childhood on Neurological Function

Anesthetic agent	Dose or duration	Study design	No. of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Midazolam (plus fentanyl)	0.07–0.94 mg/kg/h for up to 38 d	Case–control	45	0.03–19.2 yr	After discontinuation of sedation, poor social interaction, decreased visual attentiveness, dystonic postures, and choreoathetosis in 11%	No sequelae 4 wk after discontinuation	Bergman et al.[68]
Midazolam (plus pentobarbital)	1–17 d	Retrospective cohort study	40	0.5–14 yr	After discontinuation of sedation, agitation, anxiety, muscle twitching, sweating, tremor in 35%. Midazolam dose of >60 mg/kg strongly associated with symptoms	Symptoms abolished by pentobarbital treatment	Fonsmark et al.[70]
Midazolam (plus opioid)	1.5–4 mg/h for 10 d	Case series	6	1–6 yr	Multifocal myocloni, dystonia, chorea, facial grimacing, tongue thrusting without seizure activity on EEG. Chemotherapy for CNS malignancies, MRI abnormalities	3–7 d	Khan et al.[72]
Midazolam (plus morphine)	0.025–0.72 mg/kg/h for 1–18 d	Cohort study	53	6 d to 11 yr	After discontinuation, prolonged sedation for up to 1 wk in 8%. Disorientation, hallucinations, and behavioral abnormalities in up to 11%	0.13–7 d	Hughes et al.[69]
Midazolam (plus opioid)	0–0.014 mg/kg/min for 4–18 d	Cohort study	15	6 wk to 2.3 yr	After discontinuation, sleeplessness, tremors, agitation, movement disorder in up to 50%. Symptoms occurred as late as 6 d after start of taper	3 d	Franck et al.[71]
Lorazepam (plus opioid)	0.1–0.4 mg/kg/h for 11–30 d	Prospective, open-label study	29	0.2–3 yr	During taper, 24% experienced agitation, irritability, abnormal movements, or hallucinations	Not specified	Dominguez et al.[73]

(*Continued*)

Table 1. Continued

Anesthetic agent	Dose or duration	Study design	No. of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Pentobarbital (plus midazolam)	1–17 d	Retrospective cohort study	40	0.5–14 yr	After discontinuation of sedation, agitation, anxiety, muscle twitching, sweating, tremor in 35%. Pentobarbital >25 mg/kg associated with symptoms	Symptoms abolished by pentobarbital treatment	Fonsmark et al.[70]
Pentobarbital (plus benzodiazepines and opioids)	1–5 mg/kg/h for 0.6–49 d	Case series	8	0.4–7 yr	During sedation, one patient (12.5%) experienced choreiform movements with athetoid features, ataxia, facial twitching. Also received mathadone and phenobarbital	1 wk	Yanay et al.[80]
Pentobarbital	1–4 mg/kg/h for 4–28 d	Case series	6	0.17–1.4 yr	None reported	Not applicable	Tobias et al.[81]
Phenobarbital (plus phenytoin)	20–1800 mg/d in mother	Case–control	172	fetal exposure	Greater need for special education, learning difficulties, lower intelligence (WAIS), decreased attention on D-2, but not CPT test in adults after fetal exposure vs. controls. No difference in memory tasks (DS, ALT)	Not applicable	Dessens et al.[82]
Phenobarbital	2.5–50 mg for 1–540 d	Cross sectional, case–control	28	Neonate	No difference in Kaufman-ABC intelligence and D-2 tests between 8- and 14-yr-old children following neonatal treatment with Phenobarbital and best-friend controls	Not applicable	Gerstner et al.[83]
Ketamine	13–56 mg/kg	Case series	18	0.07–7 yr	After inadvertent overdose, prolonged sedation and respiratory depression	Sedation for 3–24 h, no neurological sequelae on follow-up, where available	Green et al.[87]

(*Continued*)

Table 1. Continued

Anesthetic agent	Dose or duration	Study design	No. of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Propofol	200 mg/h for 48 h in utero	Case report	1	Premature neonate 33 wk GA	Prolonged sedation, no other neurological sequelae reported	12 h	Bacon et al.[99]
Propofol	10.9 mg/kg/h for 11 d	Case report	1	23 mo	Restlessness, muscle twitching limbs, functional blindness	Motor function impaired for 2 wk, blindness for 33 d	Lanigan et al.[101]
Propofol	Median infusion 2.7 mg/kg/h for >24 h	Case series	20	Median age 3.3 yr	No neurological sequelae	Not applicable	Macrae and James[100]
Propofol	6–18 mg/kg/h for 2–4 d	Case report	2	2.5 and 4 yr	Muscle weakness, twitching,	9–18 d, full recovery	Trotter et al.[102]
Propofol	10 mg/kg/h for 54 min	Case report	1	6 yr	Seizure, ataxia, hallucinations starting 44 h after discontinuation of propofol	5 d, recovered without overt long-term sequelae	Bendiksen et al.[103]
Isoflurane	13–497 MAC-h	Cohort study	10	0.06–19 yr	Agitation, nonpurposeful movement in 50% of patients; all received >70 MAC-h isoflurane, plus benzodiazepines and opioids	Symptoms responded to treatment advocated for opioid withdrawal	Arnold et al.[116]
Isoflurane	0.25%–1.5% for 1–76 h	Case series, case–control	12	0.5–10 yr	Transient ataxia, agitation, hallucinations, and confusion after isoflurane administration >24 h; no symptoms after benzodiazepines or isoflurane <15 h	Normal follow-up exam 4–6 wk after discharge	Kelsall et al.[117]
Isoflurane	81 MAC-h	Case report	1	2.5 yr	Self-limiting, fine tremor in patient with myasthenia	46 h	McBeth et al.[118]
Isoflurane	0.4%–0.9% for 6–8 d	Case series	3	4–11 yr	Temporary involuntary movements, myoclonia, brief seizures, and ataxia	Resolution of symptoms within 4–5 d	Sackey et al.[119]
Isoflurane (plus midazolam and morphine)	0.5%–1% for 4 d	Case report	1	7 yr	Disorientation, hallucinations, agitation, seizure	5 d; reportedly normal behavior	Hughes et al.[115]
Sevoflurane	8% during induction	Prospective study	20	1.1–8.4 yr	Seizure-like movement and epileptiform EEG in 10%, no neuro exam	Not applicable	Conreux et al.[141]
Sevoflurane	8% during induction	Prospective study	31	2–12 yr	Epileptiform discharge in 88% with controlled ventilation and 20% with spontaneous breathing. No neuro exam	Not applicable	Vakkuri et al.[142]

(*Continued*)

Table 1. Continued

Anesthetic agent	Dose or duration	Study design	No. of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Sevoflurane	7% during induction	Prospective, randomized trial	45	2–12 yr	No seizure activity on induction. Neurological exam not performed	Not applicable	Constant et al.[143]
Sevoflurane	2% after intravenous thiopental	Prospective study	30	3–8 yr	No epileptiform EEG activity. Neurological exam not performed	Not applicable	Nieminen et al.[144]
Sevoflurane	Dose not specified	Meta-analysis of prospective studies in one center	791	3.3 ± 2.1 to 6.9 ± 2.4 yr	Increased "maladaptive" behavior in children, who were younger, and whose parents were more anxious on induction	Assessment up to 14 d postoperatively	Kain et al.[36]
Sevoflurane or halothane	2%–4% for 22 ± 17 min/1%–2% for 22 ± 15 min	Prospective, randomized trial	120	3.3 ± 2.6 to 4 ± 2.9 yr	Negative behavioral changes, such as temper tantrums, loss of appetite or sleep disturbance in 38% for up to 30 d; no difference between sevoflurane or halothane	Assessment up to 30 d postoperatively	Keaney et al.[35]
Sevoflurane or halothane	Doses not specified; outpatient surgery	Double-blinded, randomized, controlled trial	102	3–10 yr	PHBQ: No difference between both anesthetics in regard to postoperative anxiety, sleep or appetite disturbance, strength, and energy	Up to 1 wk postoperatively	Kain et al.[37]
Pentobarbital, scopolamine, ether, nitrous oxide, and/or cyclopropane	Doses not specified; otolaryngological surgery	Survey study	612	2 to over 12 yr	Parental assessment: Negative behavioral changes, such as night terrors, temper tantrums, fears, bed-wetting most prevalent in under 3 yr group (57%) compared with older group (8%)	Questionnaires mailed to parents 2 mo postoperatively	Eckenhoff[28]
Pentobarbital, scopolamine, morphine, and ether or nitrous oxide	Doses not specified; otolaryngological, dental, or ophthalmological surgery	Survey, case–control	290	1–15 yr	No differences in psychological upset after anesthesia, surgery, and hospitalization compared with siblings or healthy controls	Interview administered to patient's mother 2 wk postoperatively	Davenport and Werry[41]

(*Continued*)

Table 1. Continued

Anesthetic agent	Dose or duration	Study design	No. of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Halothane or ketamine	Dose not specified; scheduled and emergency surgery	Prospective randomized study, survey	103	1–12 yr	Parental assessment: Fear of strangers, sleep disturbance, nightmares, or bed wetting in 38% under 4 yr vs. 16% in 4-yr-olds and over	Parental assessment 1 mo postoperatively	Modvick et al.[30]
Thiopental, halothane, or methohexital induction and halothane, nitrous oxide maintenance	Methohexital 15 mg/kg PR, otherwise not specified; routine day-case ENT surgery	Survey study	86	2–10 yr	PHBQ: Problematic behavioral changes in 51% at 1 d and 34% at 1 mo postoperatively. Temper tantrums tended to be more common following stormy induction vs. calm induction of anesthesia	Questionnaires given to parents to report behavior 1 d, 1 wk, and 1 mo postoperatively	Kotiemi et al.[32]
Thiopental or propofol, isoflurane, or halothane or enflurane. Midazolam or diazepam premed	Doses not specified; ENT or ophthalmological procedures with mean anesthesia time of 32.8 ± 17.9 min	Multicenter survey	551	0.3–13.4 yr	PHBQ: Behavioral problems in 47% on day of surgery, 9% after 4 wk, including attention seeking, crying, temper tantrums, sleep problems, anxiety	Questionnaires given to parents to report behavior up to 4 wk postoperatively	Kotiemi et al.[33,34]
Halothane/ nitrous oxide	Dose not specified; elective minor head and neck surgery	Survey study	122	1–8 yr	Parental assessment: Behavioral abnormalities in up to 88% of children awake during induction and 58% of children asleep during induction	Questionnaires mailed to parents within first postoperative month	Meyers and Muravchick[31]

ALT= Associated Learning Task; CPT= Continuous Performance Task for sustained attention; D-2= selective attention test; DS= Digit Span memory test; PNBQ= Vernon Post Hospitalization Behavioral Questionnaire; WAIS= Wechsler Adult Intelligence Scale.

mechanism remains unknown, psychological factors, rather than structural brain abnormalities, are generally believed to be the underlying etiology.[29,30,39] Importantly, the addition of a benzodiazepine before general anesthesia did not exacerbate postoperative behavioral abnormalities, as expected for a cytotoxic etiology, but rather significantly reduced abnormal behavioral symptoms.[40] However, although most postoperative behavioral studies rely on parental assessment of the child, no continuing professional observations and long-term neurocognitive assessments were incorporated in these studies. Therefore, the permanence of these neurological abnormalities remains uncertain. Moreover, when patients' postoperative behavior was compared with siblings or healthy controls, no difference was observed.[41]

Anesthesia in Neonates and Young Children

Neurodevelopmental outcome, as evaluated with validated neurocognitive assessment tools, has not been studied in healthy neonates or infants undergoing anesthesia for elective surgery. Conversely, several studies have evaluated long-term neurodevelopment in critically ill neonates after surgical procedures involving general anesthesia, including ligation of patent ductus arteriosus, repair of esophageal atresia, inguinal hernia repair, neurosurgical operations, laparotomy, or tracheotomy.[42–51] However, the anesthetic regimen was not specified in any of these studies. Long-term neurodevelopmental impairment, such as a reduction in IQ, increased incidence of cerebral palsy, deafness, or blindness, has frequently been observed.[45–49,51] Greater severity of illness and coexisting, congenital abnormalities

Table 2. Clinical Research Reports on the Effects of Neonatal or Infant Surgery and Anesthesia on Neurological Function

Study design	Study group	Control group	No. of subjects	Age during exposure	Age during neurological assessment	Neurological assessment tool	Neurological sequelae in study group	Reference
Case–control study	PDA ligation, inguinal hernia repair, GI surgery, neurosurgery, tracheotomy	No surgical intervention	221	First hospitalization for <27 wk PCA, ELBW	5 yr	Neurological examination, WPPSI-R	Increased incidence of cerebral palsy, blindness, deafness, WPPSI-R >3 SD below mean	The Victorian Infant Collaborative Study Group[46]
Case series	Repair esophageal atresia	None, comparison with general population	36	Neonatal	10.2 yr	WISC-RN, ADQC, CBCL, TRF	10% reduction in IQ, SE five times as frequent; subgroup without major associated congenital anomalies had normal IQ	Bouman et al.[48]
Case series	Repair esophageal atresia	None, comparison with general population	34	Neonatal	12.7 yr	WISC, HFT, Rohrschach test	No statistical difference in IQ compared with age- and gender-matched general population	Lindahl et al.[42]
Cohort study, case–control study	PDA ligation	Indomethacin treatment	340	84% neonatal (25–29 wk PCA), ELBW	18 mo	Neurological examination, BSID2	Increase in cerebral palsy, cognitive delay, hearing loss, bilateral blindness	Kabra et al.[51]
Cohort study, case–control study	Laparotomy	Peritoneal drain placement	3725	Neonatal, ELBW	18–22 mo	Neurological examination, BSID2	Blinded assessor: Higher frequency of CP and lower BSID 2; no difference between medically treated patients with or without NEC	Hintz et al.[49]
Case–control study	Laparotomy	Peritoneal drain placement	78	29 wk PCA, ELBW	18–22 mo postterm	Neurological examination, BSID2	Less neurodevelopmental impairment and lower mortality	Blakely et al.[50]
Case–control study	NEC	No NEC	802	30 wk PCA, VLBW	20 mo postterm	SBIS, BSID	No blinded assessor: No significant difference in BSID scores; impairment more prevalent in survivors of most severe form of NEC, however, not stratified by surgical or medical management	Walsh et al.[43]
Case–control study	NEC requiring laparotomy	No NEC or NEC managed medically	115	26–27 wk PCA, VLBW	12 mo, 3 yr, and 5 yr PCA	GMDS, SBIS	No blinded assessor: Higher incidence of neurodevelopmental impairment; use of inotropes and TPN dependence more prevalent after laparotomy	Tobiansky et al.[45]
Case–control study	NEC requiring laparotomy	Gestational age-, birthweight matched controls	30	26 wk PCA, ELBW	5 and 7 yr	GMDS, SBIS, CBCL, Peabody tests	No blinded assessor: NDI in 70% of survivors of NEC vs. 25% in age-matched controls. NDI after laparotomy for NEC 66.6% vs. 9.1% after NEC managed medically. Hypotension requiring inotropes more prevalent after laparotomy	Chacko et al.[47]

(*Continued*)

Table 2. Continued

Study design	Study group	Control group	No. of subjects	Age during exposure	Age during neurological assessment	Neurological assessment tool	Neurological sequelae in study group	Reference
Case–control study	NEC requiring laparotomy	NEC managed medically	18	Neonatal, VLBW	8, 15 mo postterm, 24 mo	BSID, INFANIB, DDST	Assessor not blinded: Higher prevalence of motor delays early after surgery; no differences detected at 2 yr of age	Simon et al.[44]
Prospective, randomized trial	ASO with DHCA	ASO with LF-CPB or general population	155	Neonatal	1, 2.5, 4, 8 yr	WISC 3, WIAT, TRF, CBCL, WCST, TOVA, Mayo Test for Apraxia of Speech, Goldman-Fristoe Test of Articulation	Lower Full-Scale IQ, Perceptual Organization, and Freedom from Distractibility scores, WIAT Reading and Mathematics Composites, Memory Screening Index, WCST, TOVA scores Most differences were <1 SD	Bellinger et al.[55,57,61]
Cohort study	Open-heart surgery	None	59	Neonatal	≥2 yr	SBIS or BSID	Cerebral palsy in 22%, mean IQ 90, but highly dependent on type of congenital heart disease	Miller et al.[53,54]
Case series	ASO	None, comparison with general population	60	Neonatal	3–14 yr	Kiphard and Schilling Body Coordination Test, Kaufman Assessment Battery for Children, Oral and Speech Motor Control Test, Nayo Test of Speech and Oral Apraxia	Assessor not blinded: Increased prevalence of neurological impairment (27%), speech impairment (40%), motor dysfunction, language impairment; no difference in intelligence	Hövels-Gürich[56,60]
Case–control study	ASO with limited DHCA	"Best friend" control group or general population	148	0–118 (median 9) days	9.1 ± 2.9 yr	WPPSI-R or WISC 3, CBCL, Movement ABC	Lower IQ than control, but still above general population mean; higher prevalence of behavioral, language expression and comprehension problems	Karl et al.[62]
Case series	Open-heart surgery	None, comparison with general population	98	Infancy	1–3 yr	PDMS, GMDS	Blinded assessor: Abnormal neurological exam in 41%, motor delay in 42%, and global developmental delay in 23%	Limperopoulos et al.[58]
Case series	HLHS	None, comparison with general population	28	Several procedures as neonates and early childhood	8.6 ± 2.1 yr	WISC 3, WJPB, VMI, CELF-R, CBCL	Assessor not blinded: Prevalence of mental retardation 18% and borderline IQ in 36%. Learning disability in over 14% of survivors. Performance IQ scores lower than verbal IQ	Mahle et al.[59]

(*Continued*)

Table 2. Continued

Study design	Study group	Control group	No. of subjects	Age during exposure	Age during neurological assessment	Neurological assessment tool	Neurological sequelae in study group	Reference
Cohort study, case–control study	Intrauterine exposure to nitrous oxide	No intrauterine exposure	159	Prenatal: third trimester	5 d postnatally	Prechtl's neurological and Brazelton's behavioral assessments	Weaker habituation to sound, stronger muscular tension and resistance to cuddle, fewer smiles	Eishima[67]
Case–control study	General or local anesthetics	No anesthetic exposure	39	Prenatal: first to third trimester	0.8–6 d postnatally	Measurement of visual-pattern preference	Prolongation of visual-pattern preference	Blair et al.[65]
Case–control study	General or local anesthetics	No anesthetic exposure	14	Prenatal: first to third trimester	4 ± 0.08 yr	PPVT, vocabulary parts of WPPS and SBIS	Lower PPVT IQ scores, no differences in WPPS or SBIS	Hollenbeck et al.[66]
Prospective, case–control study	Thiopental, nitrous oxide for general anesthesia	Lidocaine 1.5% for epidural analgesia	30	Perinatal for cesarean section	1–7 d	Neurological assessment as per Prechtl and Beintema	Blinded assessor: Abnormal neurologic activity for up to 7 days in 47%, regardless of group assignment	Hollmen[64]
Survey study	General anesthesia for general surgery, ENT, gastroenterology, plastics surgery, orthopedics	None, some sibling controls	1027	3–12 yr	3 and 30 d postanesthesia	PHBQ	Behavioral changes in 24% on day 3 after surgery, 16% on day 30, including anxiety and regression, apathy or withdrawal, and separation anxiety	Stargatt et al.[38]

ADQC = Abbreviated Depression Questionnaire for Children Self Assessment; ASO = arterial switch operation; BSID = Bayley Scales of Infant Development; CBCL = Achenbach Child Behavior Checklist Parental Assessment; CELF-R = Clinical Evaluation of Language Fundamentals-Revised; DDST = Denver Developmental Screening Test; DHCA = deep hypothermic circulatory arrest; ELBW = extremely low birth weight (<1000 g); GMDS = Griffiths Mental Development Scales; INFANIB = Infant Neurological International Battery; LF-CPB = low flow-cardiopulmonary bypass; MDI Bayley = Mental Development Index; Movement ABC = Movement Assessment Battery for Children; NDI = neurodevelopmental impairment; PDI = Bayley Psycomotor Developmental Index; PDMS = Peabody Developmental Motor Scales; PHBQ = Vernon Post Hospitalization Behavior Questionnaire; PPVT = Peabody Picture Vocabulary Test; SBIS = Stanford-Binet Intelligence Scales; TOVA = Test of Variables of Attention; TRF = Teacher's Report Form; VMI = Developmental Test of Visual Motor Integration; WCST = Wisconsin Card Sorting Test of problem solving; WJPB = Woodcock-Johnson Psychoeducational Battery; VLBW = very low birth weight (≤1500 g); WIAT = Wechsler Individual Achievement Test; WISC 3 = Wechsler Intelligence Scale for Children, Third Edition; WISC-RN = Wechsler Intelligence Scale for Children; WPPS-R = Revised Wechsler Preschool and Primary Scales for Intelligence.

were associated with worsening neurological outcome.[43,48] In an attempt to at least partially control for severity of illness, several case–control studies compared neurodevelopmental outcome in survivors of surgical therapy of necrotizing enterocolitis and patent ductus arteriosus with patients undergoing medical management for the same illness. When compared with age-matched controls or medically treated patients in the same cohort, several investigators noticed an impairment in neurocognitive function in surgically treated survivors of laparotomy or thoracotomy,[45–47,49,51] whereas others were unable to find these differences.[42,44,50] However, it is difficult to separate the effects of neonatal stress and surgery from the effects of the anesthetics. Moreover, study designs did not include randomized, controlled trials, but were rather designed as cohort studies or case–control studies. It is therefore possible that, due to selection bias, some of the extremely premature neonates who needed surgery had concomitant illnesses and were therefore sicker than their matched controls. This notion is underscored by the fact that some of the studies identified longer periods of hypotension, more common use of inotropic support, and longer periods of total parenteral nutrition in the postsurgical patients.[45,47] Accordingly, a prospective randomized trial of 117 preterm infants with necrotizing enterocolitis who were either assigned to laparotomy or peritoneal drainage did not find any difference in patient survival and early outcomes.[52]

Another patient population that has been followed for evaluation of long-term neurocognitive development is neonates and infants undergoing open-heart surgery for congenital heart disease, such as hypoplastic left heart syndrome, transposition of the great arteries, or tetralogy of Fallot.[53–63] Neurocognitive impairment has been documented in many of these studies, compared with the general population,[53–61,63] or with "best friend" control subjects.[62] However, anesthetic regimen was not specified for any of these studies and confounding factors include preoperative neurological lesions, preexisting or perioperative hypoxia and hypotension, and chronic postoperative hypoxia in many of these patients. Interestingly, in the largest trial, the Boston Circulatory Arrest Trial, with patient follow-up for 8 yr after arterial switch operation, many outcome measures in a battery of neurodevelopmental tests were within normal population limits, despite major corrective cardiac surgery as neonates.[61]

Table 3. Preclinical Research Reports on the Effects of Anesthetic Exposure In Neonatal Animals on Neuronal Structure and Subsequent Neurological Function

Anesthetic agent	Dose and duration	Species	Age	Histopathology	Neurocognitive deficits	Reference
Clonazepam	0.5–4 mg/kg IP	Rat (Sprague-Dawley)	P7	Increased neurodegeneration	Not assessed	Ikonomidou et al.[74]
Clonazepam	0.5–4 mg/kg IP	Rat (Wistar)	P7	Increased apoptotic neurodegeneration 24 h after exposure	Not assessed	Bittigau et al.[75]
Diazepam	10–30 mg/kg IP	Rat (Sprague-Dawley)	P7	Increased neurodegeneration	Not assessed	Ikonomidou et al.[74]
Diazepam	5 mg/kg IP	Rat (Wistar)	P7	No increase in neurodegeneration 24 h after exposure	Not assessed	Bittigau et al.[75]
Diazepam	10–30 mg/kg IP	Rat (Wistar)	P7	Increased apoptotic neurodegeneration 24 h after exposure, ameliorated by flumazenil	Not assessed	Bittigau et al.[75]
Diazepam	5 mg/kg SC	Mouse (NMRI)	P10	No increased neurodegeneration in parietal cortex 24 h after exposure, increased neurodegeneration in laterodorsal thalamus	No behavioral impairment or neurocognitive deficits in adult mice 2 mo after exposure	Fredriksson et al.[76]
Midazolam	9 mg/kg IP	Rat (Sprague-Dawley)	P7	No increase in apoptotic neurodegeneration 18 h after exposure	Not assessed	Jevtovic-Todorovic et al.[77]
Midazolam	9 mg/kg SC	Mouse (C57BL/6)	P7	Increased neuroapoptosis in cortex and caudate-putamen	Not assessed	Young et al.[79]
Midazolam	9 mg/kg	Mouse	P5	Increased apoptotic neurodegeneration in caudate/putamen and cortex, significantly reduced by pilocarpine pretreatment	Not assessed	Olney et al.[122]
Midazolam	0.25–25 μg/mL	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest	No effects on neuronal cell survival	Not applicable	Vutskits et al.[78]
Midazolam	3–9 mg/kg IP	Rat (Sprague-Dawley)	P1–14	No increase in neuroapoptosis	Not assessed	Yon et al.[126]
Pentobarbital	5–10 mg/kg IP	Rat (Wistar)	P7	Widespread neurotoxicity	Not assessed	Bittigau et al.[75]
Phenobarbital	20–30 mg/kg IP	Rat (Wistar)	P7	No increase in neurodegeneration 24 h after exposure	Not assessed	Bittigau et al.[75]
Phenobarbital	40–100 mg/kg IP	Rat (Wistar)	P7	increased apoptotic neurodegeneration 24 h after exposure, ameliorated by β-estradiol	Not assessed	Bittigau et al.[75]
Phenobarbital	50 mg/kg IP	Rat (Wistar)	P7	Increased apoptotic neurodegeneration 24 h after exposure, ameliorated by β-estradiol	Not assessed	Asimiadou et al.[84]
Thiopental	5–25 mg/kg SC	Mouse (NMRI)	P10	No increase in neurodegeneration	No impairment in behavior or learning in adult mice 45 or 53 d after exposure	Fredriksson et al.[85]
Ketamine	single dose of 25–75 mg/kg IP	Rat (Sprague-Dawley)	P7	No increase in neurodegeneration 24 h after exposure	Not assessed	Hayashi et al.[88]
Ketamine	Four doses of 25 mg/kg IP every 90 min	Rat (Sprague-Dawley)	P7	No increase in neurodegeneration 24 h after exposure	Not assessed	Hayashi et al.[88]

(*Continued*)

Table 3. Continued

Anesthetic agent	Dose and duration	Species	Age	Histopathology	Neurocognitive deficits	Reference
Ketamine	Seven doses of 25 mg/kg IP every 90 min	Rat (Sprague-Dawley)	P7	Increased apoptotic neurodegeneration 24 h after exposure, especially temporal cortex and thalamus	Not assessed	Hayashi et al.[88]
Ketamine	Seven doses of 10 mg/kg IP every 90 min	Rat (Sprague-Dawley)	P7	No increase in neurodegeneration 24 h after exposure, plasma ketamine levels close to human anesthesia	Not assessed	Scallet et al.[89]
Ketamine	Seven doses of 25 mg/kg IP every 90 min	Rat (Sprague-Dawley)	P7	Increased apoptotic neurodegeneration 24 h after exposure, plasma ketamine levels seven times higher than during human anesthesia	Not assessed	Scallet et al.[89]
Ketamine	20 mg/kg IP	Rat (Sprague-Dawley)	P7	No increase in neurodegeneration 24 h after exposure, plasma ketamine levels close to human anesthesia	Not assessed	Scallet et al.[89]
Ketamine	2.5 mg/kg SC × 2 daily for 4 d	Rat (Long-Evans hooded)	P1–4	No increase in neurodegeneration; ketamine ameliorated pain-induced neurodegenerative effects	No impairment in adult rats; ketamine ameliorated the pain-induced decrease in acquisition of visual-spatial clues, impairment of short-term and long-term memory, and increase in pain latencies	Anand et al.[91]
Ketamine	Seven doses of 20 mg/kg IP every 90 min	Rat	P7	Increased apoptotic neurodegeneration 24 h after exposure	Not assessed	Ikonomidou et al.[90]
Ketamine	1.25–2.5 mg/kg SC	Mouse (ICR)	P7	No increase in neurodegeneration	No gross neurobehavioral abnormalities 7 d after exposure	Rudin et al.[92]
Ketamine	5–40 mg/kg SC	Mouse (ICR)	P7	Increased neurodegeneration 1–7 d after exposure	No gross neurobehavioral abnormalities 7 d after exposure	Rudin et al.[92]
Ketamine	10 mg/kg SC	Mouse (C57BL/6)	P7	No increase in neuroapoptosis	Not assessed	Young et al.[79]
Ketamine	20–40 mg/kg SC	Mouse (C57BL/6)	P7	Increased neuroapoptosis in cortex and caudate-putamen; no hypoxia, but respiratory alkalosis	Not assessed	Young et al.[79]
Ketamine + midazolam	40 mg/kg + 9 mg/kg SC	Mouse (C57BL/6)	P7	Increased neuroapoptosis in cortex and caudate-putamen	Not assessed	Young et al.[79]
Ketamine	50 mg/kg SC	Mouse (NMRI)	P10	No increased neurodegeneration in laterodorsal thalamus 24 h after exposure, increased neurodegeneration in parietal cortex	Abnormal behavior, impaired learning acquisition, and memory retention in adult mice 2 mo after exposure	Fredriksson et al.[76]

(*Continued*)

Table 3. Continued

Anesthetic agent	Dose and duration	Species	Age	Histopathology	Neurocognitive deficits	Reference
Ketamine	20–50 mg/kg/h for 24 h	Rhesus monkey	Prenatal: E122	Increased neurodegeneration in frontal cortex, but not hippocampus, thalamus, striatum, and amygdala; ketamine plasma levels twice as high as in humans	Not assessed	Slikker et al.[93]
Ketamine	20–50 mg/kg/h for 24 h	Rhesus monkey	P5	Increased neurodegeneration in frontal cortex, but not hippocampus, thalamus, striatum, and amygdala; ketamine plasma levels 3–5 times higher than in humans	Not assessed	Slikker et al.[93]
Ketamine	20–50 mg/kg/h for 24 h	Rhesus monkey	P35	No increase in neurodegeneration; ketamine plasma levels 10 times higher than in humans	Not assessed	Slikker et al.[93]
Ketamine	20–50 mg/kg/h for 3 h	Rhesus monkey	P5	No increase in neurodegeneration	Not assessed	Slikker et al.[93]
Ketamine	0.1–1 μM for 48 h	Sprague-Dawley Rat, primary forebrain culture	Harvest P1	No increase in DNA fragmentation	Not applicable	Wang et al.[94]
Ketamine	10–20 μM for 48 h	Sprague-Dawley Rat, primary forebrain culture	Harvest P1	Increased DNA fragmentation	Not applicable	Wang et al.[94]
Ketamine	10 μM for 2 h	Sprague-Dawley Rat, primary forebrain culture	Harvest P1	No increase in DNA fragmentation	Not applicable	Wang et al.[94]
Ketamine	10 μM for 6–48 h	Sprague-Dawley Rat, primary forebrain culture	Harvest P1	Increased DNA fragmentation	Not applicable	Wang et al.[94]
Ketamine	1 μM for 24 h	Rhesus monkey, primary frontal cortical culture	Harvest P3	No increase in DNA fragmentation	Not applicable	Wang et al.[95]
Ketamine	10–20 μM for 24 h	Rhesus monkey, primary frontal cortical culture	Harvest P3	Increased DNA fragmentation	Not applicable	Wang et al.[95]
Ketamine	10 μM for 2 h	Rhesus monkey, primary frontal cortical culture	Harvest P3	No change in mitochondrial function	Not applicable	Wang et al.[95]
Ketamine	10 μM for 6–24 h	Rhesus monkey, primary frontal cortical culture	Harvest P3	Decreased mitochondrial function	Not applicable	Wang et al.[95]
Ketamine	0.01–5 μg/mL for 8 h	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest	No decrease in neuronal cell survival	Not applicable	Vutskits et al.[96]
Ketamine	10–40 μg/mL for 1 h	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest	Increased neuronal cell loss 24 h after exposure	Not applicable	Vutskits et al.[96]
Ketamine	1 μg/mL for >48 h	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest	Increased neuronal cell loss	Not applicable	Vutskits et al.[96]
Ketamine	5 μg/mL for 4 h or 2 μg/mL for 8 h	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest	Decrease in dendritic length and number of branches	Not applicable	Vutskits et al.[96]
Ketamine	≥20 μg/mL for 1 h, or ≥10 μg/mL for 8 h, or ≥100 μg/mL for 24h	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest, exposure DIC6	Increase in neuronal cell loss starting 24 h after exposure and decrease in dendritic length and branching after 72 h	Not applicable	Vutskits et al.[97]
Ketamine	25 mg/kg SC	Mouse (NMRI)	P10	No increase in neurodegeneration	No alteration in behavior, but learning impaired in adult mice 53 d after exposure	Fredriksson et al.[85]

(*Continued*)

Table 3. Continued

Anesthetic agent	Dose and duration	Species	Age	Histopathology	Neurocognitive deficits	Reference
Ketamine + thiopental	25 mg/kg + 5 mg/kg SC	Mouse (NMRI)	P10	Increased neurodegeneration 24 h after exposure	Disruption in spontaneous activity and learning in adult mice	Fredriksson et al.[85]
Ketamine + propofol	25 mg/kg + 10 mg/kg SC	Mouse (NMRI)	P10	Increased neurodegeneration 24 h after exposure	Disruption in spontaneous activity and learning in adult mice	Fredriksson et al.[85]
Propofol	10 mg/kg SC	Mouse (NMRI)	P10	No increase in neurodegeneration	No impairment in behavior or learning in adult mice 45 or 53 d after exposure	Fredriksson et al.[85]
Propofol	60 mg/kg SC	Mouse (NMRI)	P10	Increased neurodegeneration	Disruption in spontaneous activity and learning in adult mice, altered anxiolysis effect by diazepam	Fredriksson et al.[85]
Propofol	1–20 μg/mL	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest	No effects on neuronal cell survival	Not applicable	Vutskits et al.[78]
Propofol	50 μg/mL	Sprague-Dawley Rat, GABAergic neuronal culture	Newborn harvest	Increased neuronal cell death	Not applicable	Vutskits et al.[78]
Propofol	5–500 μM for 2–24 h	Chick, neuronal explant culture	Harvest E8, exposure DIC 1	Dose-dependent neurite growth cone collapse	Not applicable	Al-Jahdari et al.[104]
Propofol	0.5 μg/mL for 8 h	Rat, GABAergic neuronal culture	Fetal harvest	No change in enzyme activity	Not applicable	Honegger et al.[105]
Propofol	2–10 μg/mL for 8 h	Rat, GABAergic neuronal culture	Fetal harvest	Dose-dependent decrease in GABAergic neuronal enzyme GAD	Not applicable	Honegger et al.[105]
Propofol	10 μg/mL for 2 h	Sprague-Dawley Rat, dissociated cortical neuronal culture	Harvest P1	No effect on neuronal survival	Not applicable	Spahr-Schopfer et al.[106]
Propofol	20–100 μg/mL for 2 h	Sprague-Dawley Rat, dissociated cortical neuronal culture	Harvest P1	Increased cell death of GABAergic neurons and glial cells	Not applicable	Spahr-Schopfer et al.[106]
Propofol	100 μg/mL for 3–10 d	Sprague-Dawley Rat, organotypic hippocampal culture	Harvest P7	No evidence for neurotoxic effects, dose 10 times higher than peak clinical dose	Not applicable	Spahr-Schopfer et al.[106]
Halothane	2.5% for 2 h	Rat (Sprague-Dawley)	Prenatal: E3, E10, or E17	Not assessed	More errors in maze task and greater footshock sensitivity in 75 d-old adult animals, exposed to halothane on E3 and E10, but not at E17	Smith et al.[113]
Halothane	Chronic exposure to 10 ppm, 8 h/d, 5 d/wk	Rat	Conception to P60	Neuronal degeneration and failure in synapse formation	Learning impairment in Y-maze utilizing foot shock and during an appetitive-reinforced, spatial discrimination task at >130 d of age; not observed in controls exposed after P60	Quimby et al.[109]

(*Continued*)

Table 3. Continued

Anesthetic agent	Dose and duration	Species	Age	Histopathology	Neurocognitive deficits	Reference
Halothane	Continuous or intermittent exposure to 50–200 ppm	Rat (Sprague-Dawley)	Conception to P28	Decrease in cerebral synapse density; dose-dependent	Not assessed	Uemura et al.[110]
Halothane	Continuous or intermittent exposure to 25–100 ppm	Rat (Sprague-Dawley)	Conception to P60	Decrease in both apical and basal dendritic length and numbers	Not assessed	Uemura et al.[111]
Halothane	Continuous or intermittent exposure to 25–100 ppm	Rat (Sprague-Dawley)	Conception to P60	Decreased synaptic density, more severe in cortex than subiculum; no difference between P5, P21, P34, or P95	No difference in T-maze performance at age 20, 40, 60, or 100 d between halothane exposed animals and controls	Uemura et al.[112]
Halothane or enflurane	1%–2% or 2%–4% for 0.5 h	Mouse (Albino)	Prenatal: E6–E17	Not assessed	Learning impairment in navigating a maze in adult mice, 6–7 wk old	Chalon et al.[114]
Isoflurane + midazolam + N_2O	0.75% + 9 mg/kg + 75% for 2–6 h	Rat (Sprague-Dawley)	7 d	Increased caspase-3 and -9 activation, no hypoxia or hypoglycemia, metabolic and respiratory alkalosis	Not assessed	Lu et al.[120]
Isoflurane	0.75% for 6 h	Rat (Sprague-Dawley)	P7	Increased caspase-3 expression, exacerbated by 75% N_2O and ameliorated by 30% or 60% xenon	Not assessed	Ma et al.[121]
Isoflurane	0.75% for 6 h	Mouse (C57BL/6), organotypic hippocampal slice	P8–9	Increased caspase-3 expression, ameliorated by 30% or 60% xenon	Not assessed	Ma et al.[121]
Isoflurane	0.75%–1.5% for 6 h	Rat (Sprague-Dawley)	P7	Dose-dependent increase in neurodegeneration	Not assessed	Jevtovic-Todorovic et al.[77]
Isoflurane + midazolam + N_2O	0.75% + 9 mg/kg + 75% for 6 h	Rat (Sprague-Dawley)	P7	Widespread increased neurodegeneration and apoptosis	no behavioral abnormalities in adult animals, but temporary learning impairment 25 and 124 d after exposure	Jevtovic-Todorovic et al.[77]
Isoflurane	1 MAC for 4 h	Rat (Sprague-Dawley)	P7	Not assessed	Abnormal fear behavior in adult animals 5 mo after exposure, learning impairment at 8 mo	Stratmann[125]
Isoflurane	0.75%–1.5% for 6 h	Rat (Sprague-Dawley)	P1–3	Significant increase in neuroapoptosis only after 1.5% isoflurane	Not assessed	Yon et al.[126]
Isoflurane	0.75%–1.5% for 6 h	Rat (Sprague-Dawley)	P10–14	No increase in neuroapoptosis	Not assessed	Yon et al.[126]
Isoflurane + midazolam + N_2O	0.75% + 9 mg/kg + 75% for 2–6 h	Rat (Sprague-Dawley)	P1–14	Increased neuroapoptosis, especially in P7 animals	Not assessed	Yon et al.[126]
Isoflurane	1.3% for 6 h	Rat	Prenatal: E21	Significant increase in neurodegeneration in retrosplenial cortex and hippocampal CA1	No difference in Morris watermaze learning task in young adulthood	Li et al.[129]

(*Continued*)

Table 3. Continued

Anesthetic agent	Dose and duration	Species	Age	Histopathology	Neurocognitive deficits	Reference
Isoflurane + midazolam + N_2O	0.75% + 9 mg/kg + 75% for 6 h	Rat (Sprague-Dawley)	P7	Increased neurodegeneration in anterior thalamus and cortex, dose-dependent reduction by melatonin	Not assessed	Yon et al.[130]
Isoflurane + N_2O	0.75% + 75% for 6 h	Rat (Sprague-Dawley)	P7	Increased apoptotic neurodegeneration, significantly reduced by dexmedetomidine coadministration	Not assessed	Sanders et al.[131]
Isoflurane	0.75% for 4 h	Mouse	P5	Increased apoptotic neurodegeneration in caudate/putamen and cortex, significantly reduced in cortex by pilocarpine pretreatment	Not assessed	Olney et al.[122]
Isoflurane	1.5% for 6 h	Mouse (CD1/C57BL/6 hybrid)	P7	Increased neurodegeneration	No behavioral impairment or neurocognitive deficits in adult mice 2 mo after exposure	Loepke et al.[117]
Isoflurane + midazolam + N_2O	0.55% + 1 mg/kg + 75% for 4 h	Swine	P5	Increased neurodegeneration in neocortex compared with controls; significantly less cell death after fentanyl-based anesthetic	Not assessed	Rizzi et al.[123]
Isoflurane + midazolam + N_2O	0.55% + 1 mg/kg + 75% for 4 h	Guinea pig	Prenatal: E35–40	Increased neurodegeneration in neocortex compared with controls; significantly less cell death after fentanyl-based anesthetic	Not assessed	Rizzi et al.[124]
Isoflurane	1.5% for 1–3 h	Sprague-Dawley rat, organotypic hippocampal slice	Harvest on P4–14, exposure DIC 7 or 14	No increase in neuronal cell death	Not applicable	Wise-Faberowski et al.[95]
Isoflurane	1.5% for 5 h	Sprague-Dawley rat, organotypic hippocampal slice	Harvest on P4–14, exposure DIC 7 or 14	Increased neuronal cell death, greatest in P7 slice cultures	Not applicable	Wise-Faberowski et al.[128]
Nitrous oxide	50%–150% for 2–6 h	Rat (Sprague-Dawley)	P7	No increase in neuronal cell death	Not assessed	Jevtovic-Todorovic et al.[77]
Nitrous oxide	50%–150% for 2–6 h	Rat (Sprague-Dawley)	P1–14	No increase in neuroapoptosis	Not assessed	Yon et al.[126]
Nitrous oxide	75% for 6 h	Rat (Sprague-Dawley)	P7	No increase in caspase-3 expression	Not assessed	Ma et al.[121]
Nitrous oxide	75% for 6 h	Mouse (C57BL/6), organotypic hippocampal slices	P8–9	Increased caspase-3 expression	Not assessed	Ma et al.[121]
Xenon	75% for 6 h	Rat (Sprague-Dawley)	P7	No increase in caspase-3 expression	Not assessed	Ma et al.[121]
Xenon	75% for 6 h	Mouse (C57BL/6), organotypic hippocampal slices	P8–9	No increase in caspase-3 expression	Not assessed	Ma et al.[121]

DIC = day in culture; E = embryonic day; IP = intraperitoneal; P = postnatal day; SC = subcutaneously.

Several case–control studies address the neurocognitive implications of prenatal anesthetic exposure *in utero*.[64–67] Abnormal neurological activity observed in neonates early after delivery included increased motor tone and decreased interaction,[67] visual test abnormalities,[65] and motor weakness.[64] Interestingly, the incidence of early neurological abnormalities after cesarean delivery did not differ between neonates exposed to general anesthesia, including thiopental and nitrous oxide, or to maternal epidural analgesia using lidocaine.[64] In a small, 4-year follow-up after prenatal exposure to anesthetics for dental procedures,[65] children

had decreased intelligence scores compared with unexposed controls, but demonstrated similar performance on tests of their vocabulary.[66] However, anesthetic exposure was not quantified, spanned from the first to the third trimester of pregnancy, and consisted of such diverse anesthetics as methohexital, penthotal, lidocaine, or carbocaine.

In summary, although several cohort studies in premature and term neonates undergoing major surgical operations involving general anesthesia demonstrate neurodevelopmental impairment later in life, none of these studies specified the anesthetic technique used. Moreover, because of the study design limitations, the effects of concomitant disease and the impact of the surgical procedure cannot be separated from the effects of anesthesia.

Although anesthetic regimen was not systematically described in the studies cited above, several reports, in animals or humans, address the effects of specific anesthetics and doses on neuronal structure and/or neurodevelopmental outcome.

Benzodiazepines

No studies were identified demonstrating neuronal degeneration or abnormal neurocognitive function in young children after brief sedation with benzodiazepines. However, there are several reports related to transient neurological abnormalities after prolonged sedation with benzodiazepines in children, which were generally attributed to withdrawal symptoms or tachyphylaxis.[68–73] In a retrospective chart review of 45 patients who had received prolonged midazolam sedation between 0.07 and 0.94 $mg \cdot kg^{-1} \cdot h^{-1}$ and fentanyl for up to 38 days, five patients (11%) were identified, ranging from 3 to 15-mo-of-age, who demonstrated poor social interaction, decreased visual attentiveness, dystonic postures, and choreoathetosis upon discontinuation of the sedation, whereas 40 patients had no neurologic abnormalities.[68] A repeat neurological examination up to 4 wk after discontinuation of sedation was normal in all children. In a prospective study in 53 critically ill neonates and children, Hughes et al. observed disorientation and hallucinations in 11% and prolonged sedation in 8% for up to 1 wk after midazolam discontinuation,[69] whereas Franck et al. found sleeplessness, agitation, and movement disorder in up to 50% in a smaller and younger cohort.[71] In a retrospective chart review of 40 patients ranging from 6 mo to 14 yr of age, Fonsmark et al.[70] observed neurological abnormalities in 35% of children after discontinuation of prolonged sedation with midazolam, pentobarbital, or a combination of the two. Neurological abnormalities were described as agitation, anxiety, muscle twitching, sweating, and tremor and were attributed to withdrawal symptoms. Symptoms were positively correlated with midazolam doses of more than 60 mg. Interestingly, although the diagnoses were diverse, half of the children who demonstrated neurological symptoms after discontinuation of sedation had preexisting CNS abnormalities, with an admission diagnosis of meningitis. In a case series of six critically ill cancer patients ranging from 1 to 6-yr-of-age, which represented 8% of the comparable intensive care unit patient population, Khan et al.[72] described multifocal myocloni, dystonia, chorea, facial grimacing, tongue thrusting, and conjugate gaze deviation in the absence of seizure activity on electroencephalogram (EEG). Because five of these patients were being sedated with midazolam and an opioid for more than 10 days, although in one patient sedation had been discontinued 1 day before the onset of symptoms, the authors identified midazolam sedation as the most likely reason for the development of the generalized movement disorder. However, they acknowledge that the etiology could have been multifactorial, because 67% of the affected patients had undergone a resection of a brain tumor, 83% received amphotericin, a known neurotoxicant, and all received chemotherapy. Moreover, tachyphylaxis to midazolam could have been a factor, because symptoms were abolished in 67% of patients by increasing midazolam and fentanyl doses. In another study, a prospective trial in 29 patients, Dominguez et al.[73] observed withdrawal symptoms in 25% of patients on discontinuation of lorazepam, which had been administered for a median duration of 21 days.

Preclinical data on neurodegeneration after benzodiazepine administration in animal models are conflicting. Studies in neonatal rat pups that received injections of diazepam 10–30 mg/kg or clonazepam 0.5–4 mg/kg demonstrated increased neurodegeneration.[74,75] In the same study, however, a lower dose of diazepam, 5 mg/kg, did not increase neuronal degeneration in rats,[75] whereas an identical dose of diazepam increased neurodegeneration in another study of neonatal mice.[76] However, this diazepam-induced neurodegeneration in neonatal mice did not lead to impaired behavior or neurocognitive performance deficits in adulthood.[76] Using midazolam, another group of researchers did not note any increase in the rate of neurodegeneration in neonatal rats for doses up to 9 mg/kg.[77] This finding was supported by *in vitro* experiments in rat GABAergic neuronal cultures, which demonstrated that midazolam did not impact neuronal development.[78] When midazolam was administered to neonatal mice, however, it triggered a neuroapoptotic response with the identical dose that was found safe in neonatal rats.[79]

Therefore, no information on long-term neurocognitive outcome is available in young children, whereas transient neurological abnormalities, generally ascribed to withdrawal symptoms, have been reported. The currently available data in animals support a dose-dependent increase in neurodegeneration after administration in small rodents, with higher susceptibility in mice compared with rats. However, even after injurious doses, neurocognitive testing does not reveal long-term neurological sequelae.

Barbiturates

Several small studies or case series in children have described transient neurological abnormalities on discontinuation of pentobarbital infusion,[70,80] such as choreo-athetoid movements, ataxia, and confusion, whereas other studies have not.[81] Many of these abnormalities were attributed to withdrawal symptoms. Long-term, prenatal phenobarbital and phenytoin exposure *in utero* led to an increase in learning abnormalities and mental retardation, but not cognitive impairment in adulthood, compared with a healthy cohort.[82] Moreover, a short-term exposure to phenobarbital as neonates did not diminish the performance on follow-up at age 8–14 yr, using tests of intelligence and attention, compared with healthy friends.[83]

In animal studies, increases in neuronal degeneration have been observed in rat pups after injections of pentobarbital 5–10 mg/kg or phenobarbital 40–100 mg/kg.[75,84] However, phenobarbital in lower doses, between 20 and 30 mg/kg, failed to increase neurodegeneration. The authors noted, though, that plasma levels for phenobarbital in rats, when given in doses sufficient to increase neurodegeneration in animals, were comparable to therapeutic plasma levels in children. Simultaneous estradiol administration prevented the neurodegenerative effects of phenobarbital.[84] Neonatal exposure to thiopental in doses between 5 and 25 mg/kg did not lead to an increase in neurodegeneration or long-term behavioral or learning impairment in mice.[85]

Hence, current evidence for the adverse neurological effects of barbiturates in humans is limited to case reports, usually attributed to withdrawal symptoms, and long-term neurological follow-up is lacking. Although no increased neurodegeneration or long-term neurocognitive impairment was seen after a neonatal exposure to thiopental in mice, barbiturate-induced neurodegeneration was dose-dependent in newborn rats, similar to benzodiazepines. Conversely, evidence from studies in mature rat models documents the neuroprotective effects of barbiturates during focal brain ischemia.[86] Neuroprotective effects of barbiturates have yet to be studied in immature animals.

Ketamine

There are no data regarding the effects of administration of clinical doses of ketamine in young children on brain structure or neurocognitive function. A case series of inadvertant ketamine overdoses in neonates and young children reported prolonged sedation for up to 24 h without neurological sequelae on follow-up examination, where available.[87] However, long-term neurocognitive assessments were not reported in this patient cohort.

In animal studies, similar to diazepam and phenobarbital, ketamine's ability to increase the rate of developmental neurodegeneration appears to be dose-dependent. When ketamine was administered to neonatal rats in a single dose of up to 75 mg/kg or in repeated doses of 10 mg/kg, no increased neuronal degeneration was detected.[88,89] However, after repeated doses of 20 or 25 mg/kg ketamine, increases of normal neurodegeneration were observed.[88–90] Plasma ketamine levels after the noninjurious, single doses of 10 mg/kg were comparable to anesthetizing doses in humans. However, plasma levels of ketamine after repeated doses of 20 mg/kg, which led to increased neurodegeneration in rats, were 7-times higher than measured during anesthesia in humans.[89] Conversely, a sedative dose of ketamine (5 mg/kg) administered to rat pups subjected to repetitive inflammatory pain did not increase neurodegeneration, but rather ameliorated the neurotoxic effects of painful stimulation on brain structure and short- and long-term memory.[91]

Neonatal mice, as shown by another group of researchers, demonstrated no increases in neurodegeneration after ketamine injections of 2.5 mg/kg or less, whereas doses of 5 mg/kg or higher increased neurodegeneration.[92] However, none of the animals, regardless of ketamine dose, demonstrated gross neurobehavioral abnormalities 1 wk after injection. In a different strain of neonatal mice, another group of investigators observed the neurodegenerative threshold of ketamine to be between 10 and 20 mg/kg. A single ketamine dose of 10 mg/kg did not increase neuroapoptosis, whereas single doses of 20 mg/kg or higher led to an increased rate of neuroapoptosis.[79] In another strain of slightly older 10-day-old mice, increased neurodegeneration was observed after 50 mg/kg ketamine, which led to abnormal behavior, impaired learning acquisition, and memory retention in adulthood.[76] The same group observed learning impairment in adult mice after a neonatal dose of 25 mg/kg and an increase in neurodegeneration and a disruption of spontaneous activity and learning in adulthood when combined with noninjurious doses of thiopental and propofol.[85] In nonhuman primates, a dose-dependent phenomenon was also recently observed.[93] In prenatal (gestational age 122 days) and neonatal (5-day-old) rhesus monkeys, a 24 h infusion of ketamine (20–50 $mg \cdot kg^{-1} \cdot h^{-1}$) significantly increased neuronal cell death. However, a ketamine infusion for 3 h did not lead to increased neurodegeneration in neonatal monkeys, and even a 24-h infusion failed to cause neuronal degeneration in older, 35-day-old animals. Ketamine neurotoxicity has also been studied using *in vitro* preparations from neonatal rats or rhesus monkeys.[94,95] The common finding of these studies was an exposure time-dependent increase in neuronal cell death. Ketamine exposure of cortical cultures for 6 h or longer led to an increase in neurodegeneration in both species, whereas shorter exposure times did not. The threshold for increased neurodegeneration in both studies was not exactly defined, but was between 2 and 6 h. Studies using a

GABAergic neuronal cell culture model have confirmed ketamine's dose and exposure-time effects on neuronal structure.[96,97] Higher ketamine concentrations led to early neuronal cell loss, whereas lower concentrations had to be administered continuously for 48 h to have a deleterious effect.

Importantly, ketamine requirements, similar to other injectable anesthetics, are 20–50 times higher in animals than in typical clinical practice. However, in a case series of neonates and young children, no neurological complications were reported on follow-up examinations after an accidental ketamine overdose of up to 50 mg/kg.[87]

In conclusion, although no information is available regarding the effects of clinical doses of ketamine on neuronal structure or neurocognitive function in young children, data obtained in developing animals point to a dose-dependent and exposure time-dependent neurodegenerative effect. Long-term neurocognitive dysfunction has thus far only been demonstrated in neonatal animals after administration of ketamine doses that led to significantly higher plasma levels than those measured during human anesthesia. However, concomitant administration of noninjurious doses of ketamine and GABAergic anesthetics significantly increased neurodegeneration and led to learning impairment in adulthood. Conversely, ketamine provides neuroprotection in adult animal models of focal brain ischemia,[98] although it has not been studied in this context in developing animals.

Propofol

The effects of propofol administration on neuronal survival and neurocognitive performance have not been formally studied in young children. Neurological performance after propofol infusion, however, has been illustrated in several case reports. Propofol sedation for 48 h in a pregnant patient with intracerebral hemorrhage did not lead to any measurable adverse effects in the newborn after emergency cesarean delivery,[99] as did propofol infusions of 2.7 $mg \cdot kg^{-1} \cdot h^{-1}$ for more than 24 h in a case series of young children.[100] However, convulsions have been observed after discontinuation of a prolonged infusion of propofol, which had been administered in doses of 6–18 $mg \cdot kg^{-1} \cdot h^{-1}$ for 3–5 days.[101,102] Another case report illustrated seizure, ataxia, and hallucinations in a 6-yr-old girl after prolonged propofol anesthesia for more than 6 h.[103] However, the authors stated that this patient recovered without long-term sequelae.

A study of the effects of propofol on neuronal structure and neurocognitive performance in mice suggests that propofol increases neurodegeneration, leading to adult, behavioral, and learning impairment in a dose-dependent manner.[85] Although neonatal exposure to propofol 10 mg/kg did not lead to neurological sequelae, increased neonatal neurodegeneration and disruption of spontaneous activity and learning in adult mice were observed after neonatal exposure to propofol 60 mg/kg or propofol 10 mg/kg plus ketamine 25 mg/kg. The higher propofol dose also led to alterations in the anxiolytic effect of diazepam in adult animals. Using *in vitro* preparations of neuronal cell cultures from immature chicks and rats, several investigators noted dose-dependent neuronal structural changes after propofol exposure.[78,104–106] Supraclinical doses of propofol induced neuronal cell death in dissociated cell culture models, but failed to demonstrate neurotoxic effects in organotypic slice cultures,[106] which more closely resemble the intact brain. Electrophysiological tests of neuronal function were not affected by propofol treatment in organotypic hippocampal slice cultures.[106] Moreover, exposure of dissociated neurons to propofol in clinically relevant concentrations for up to 3 days failed to affect neuronal survival and arborization.[106] Certain abnormalities, however, were associated with propofol administration, such as decreases in glutamic acid decarboxylase activity after 8 h of exposure[105] and changes in dendritic development after 4 h of exposure.[78]

In conclusion, no prospective studies have examined the effects of propofol on neuronal structure and neurocognitive outcome in young children, whereas several case reports detail short-term neurological abnormalities without long-term neurocognitive impairment. However, detailed follow-up has not been conducted in this patient population. A study in neonatal mice points to propofol's dose-dependent neurodegenerative properties, leading to behavioral and learning abnormalities, which are exacerbated by coadministration of ketamine. Animal studies using *in vitro* preparations demonstrate only subtle changes, whereas current evidence fails to reveal injurious effects of propofol on neuronal survival, arborization, and electrophysiological function. During brain ischemia, propofol has demonstrated neuroprotective properties in adult animal models,[107] which has yet to be confirmed in immature animals.

Etomidate

No human or animal studies could be identified examining the effects of etomidate on neuronal structure or neurocognitive performance. Etomidate, however, has been shown in adult animals to possess neuroprotective effects during brain ischemia.[108] This phenomenon has yet to be studied in newborn animals.

Halothane

No prospective studies have been conducted in children evaluating neuronal structure or neurocognitive outcome after halothane exposure early in life. Transient behavioral abnormalities, such as fear of strangers, temper tantrums, attention seeking, sleep disturbance, enuresis, and anxiety have been described after pediatric halothane anesthesia.[30,31,33,35,37]

Symptoms were most pronounced immediately postoperatively and significantly diminished over the first month after the operation. Laboratory experiments into halothane-induced neurotoxicity either used prolonged, subanesthetic exposure paradigms *in utero* until several weeks postnatally[109–112] or brief prenatal exposure to anesthetic doses.[113,114] Prenatal halothane exposure in clinical doses between gestational day 3 and 17 consistently led to learning impairment in adulthood, whereas subclinical doses decreased synaptic density, but lacked consistent neurocognitive dysfunction.[112,113]

Isoflurane

Prospective studies on neuronal structure or neurocognitive performance after isoflurane anesthesia in young children have not been published. However, several reports noted transient neurological abnormalities after prolonged sedation with isoflurane in the intensive care setting. In a case report, a 7-yr-old child exposed to 0.5%–1% isoflurane sedation for 4 days presented with disorientation, hallucinations, agitation, and seizure on discontinuation and resolution of symptoms within 5 days.[115] Concomitant medications included midazolam and morphine. A small prospective study reported on 10 patients, ranging in age from 3 wk to 19 yr, who required isoflurane sedation for prolonged mechanical ventilation due to pulmonary pathologies.[116] After discontinuation of isoflurane, transient agitation and nonpurposeful movements were noted in 50% of these patients, all of whom had received in excess of 70 MAC-h of isoflurane. Although all patients were simultaneously treated with a variety of benzodiazepines and opioids, the authors attributed the neurological symptoms to an "isoflurane abstinence syndrome" and recommended gradual weaning after prolonged administration. In a retrospective review of 6-mo to 10-yr-old children requiring sedation for mechanical ventilation, patients who had received isoflurane for more than 24 h experienced transient ataxia, agitation, hallucinations, and confusion on emergence, whereas patients who received benzodiazepines or isoflurane for $<$15 h did not.[117] Four to six weeks after hospital discharge, neurological examinations were normal in all children. In a case report of a 3-yr-old patient requiring prolonged mechanical ventilation secondary to pneumonia and congenital myasthenia gravis with 81 MAC-h of isoflurane, a self-limiting, fine tremor of all four extremities was observed for 24 h after discontinuation of isoflurane.[118] In another case series of three children requiring prolonged isoflurane sedation because of failed sedation with escalating doses of opioids and benzodiazepines, a 4-yr-old patient without prior CNS abnormalities developed temporary involuntary movements and ataxia after discontinuation of isoflurane, after 187 h of administration.[119] However, the patient was simultaneously treated with several other medications, including morphine, midazolam, S-ketamine, clonidine, propofol, and droperidol. A 12-yr-old patient who was sedated with isoflurane for 6 days experienced transient myoclonus on discontinuation of isoflurane. A 9-yr-old child was sedated with 0.9% isoflurane for 8 days for an intractable seizure disorder. No overt neurological abnormalities were observed for any of the patients on follow-up, however, no long-term neurological assessments were described.[119]

In neonatal animal models, isoflurane has been linked to apoptotic neurodegeneration in newborn rats, mice, guinea pigs, and piglets,[120–126] with most data being available in 7-day-old mice or rats. In rats, a 6-h exposure to an anesthetic combination of isoflurane, midazolam, and nitrous oxide has been demonstrated to induce widespread apoptotic neurodegeneration in newborn animals, followed by impairment in learning and memory retention tests later in adulthood.[77] The neonatal anesthetic combination, however, did not affect overall growth, sensory motor ability, attention, and spontaneous locomotion. Preliminary data in neonatal rats from another research group indicate that isoflurane, when administered for 4 h as a single anesthetic drug, alters fear conditioning and spatial learning in adulthood.[125] However, preliminary data obtained in mice demonstrate intact spatial learning, memory retention, and behavior in adult mice after a 6-h, 1.5% isoflurane exposure as neonates.[127] Both *in vitro* and *in vivo* experiments in neonatal rodent models point to a narrow time window for isoflurane-induced neurotoxicity. In an *in vitro* model of the newborn rat brain, organotypic hippocampal slices from 7-day-old pups were susceptible to isoflurane-induced neurodegeneration, whereas slices from 4 or 14-day-old pups were not.[128] Moreover, preliminary data in rats indicate that a 6 h isoflurane anesthetic in pregnant dams at the third trimester of gestation did not increase, but rather decreased neuronal cell death in rat embryos and pups and improved their spatial memory as adolescents.[129] However, preliminary data corroborate isoflurane-induced neurodegeneration in two other species. Guinea pig embryos demonstrated a dramatic increase in neurons expressing the cell suicide marker caspase 3 after a 4 h anesthetic with isoflurane, nitrous oxide, and midazolam *in utero* at 35–40 days gestation.[124] Interestingly, compared with this triple combination, neuronal suicide was dramatically decreased in guinea pig embryos whose mothers were exposed only to fentanyl for the same period of time. Similar preliminary data were presented for neonatal piglets.[123] The cell suicide marker caspase 3 was significantly increased in 5-day-old piglets, which were anesthetized with isoflurane, nitrous oxide, and midazolam and mechanically ventilated for 4 h. Animals, however, which received only fentanyl for the same time period, demonstrated a dramatic decrease in caspase 3 activity, compared with the triple combination. Several

studies have addressed how to mitigate isoflurane-induced neurodegeneration. Melatonin, when given to neonatal rats during an anesthetic of isoflurane, nitrous oxide, and midazolam, caused a dose-dependent reduction in the severity of anesthesia-induced neurodegeneration.[130]

The coadministration of the noble gas xenon prevented isoflurane-induced neurodegeneration during a 6 h exposure to 0.75% isoflurane in neonatal rats.[121] There are preliminary data for the α_2-agonist dexmedetomidine to inhibit isoflurane-induced neuroapoptosis in neonatal rats exposed to 0.75% isoflurane for 6 h.[131] In neonatal mice, preliminary data show that pretreatment with the muscarinic agonist pilocarpine reduced neuroapoptosis induced by an isoflurane exposure of 0.75% for 4 h.[122] However, pilocarpine's therapeutic margin might be limited by its ability to induce status epilepticus with concomitant neuronal degeneration.[132–134]

Contrary to the neurodegenerative effects, isoflurane was found to be neuroprotective during hypoxia-ischemia using *in vivo* and *in vitro* animal models of the developing brain.[135–137]

Thus, isoflurane has been shown in multiple developing animal models to increase baseline apoptotic neuronal degeneration. Strategies are being developed in the laboratory to mitigate the neurodegeneration. The long-term effects of neonatal isoflurane anesthesia remain controversial. Abnormal effects seem to be specific to the particular test used and to the species studied. In humans, although anecdotal data suggest at least transient neurological sequelae after prolonged exposure, no human studies have been completed examining the long-term effects of isoflurane on the developing brain. During ischemic periods, however, isoflurane administration protects neurons in the developing brain.

Desflurane

No human or animal studies could be identified that examined neuronal structure or neurocognitive performance after administration of desflurane. However, desflurane has been shown to protect the developing brain during episodes of hypoxia-ischemia in a hypothermic cardiopulmonary bypass brain ischemia model in piglets.[138,139]

Sevoflurane

Sevoflurane's effects on neuronal structure and neurocognitive performance have not been studied in humans or animals. However, numerous case reports (reviewed in Ref. 140) and several studies[141,142] have reported epileptiform EEG and seizure activity during induction of anesthesia with sevoflurane, whereas other studies have failed to document this phenomenon.[143,144] Moreover, sevoflurane anesthesia during surgery in young children has been associated with postoperative behavioral changes, such as increased temper tantrums, sleep disturbance, and loss of appetite.[35–37,38] whereas these symptoms were described as transient, no long-term neurocognitive assessment has been conducted for these patients. Contrasting these deleterious effects of sevoflurane, preliminary data in neonatal mice suggest that sevoflurane protects developing neurons during brain ischemia.[145]

Thus, although sevoflurane is the most prevalent volatile anesthetic in pediatric anesthesia, there are no data regarding neuronal structure or neurocognitive function after sevoflurane administration in newborn humans or animals. However, sevoflurane can lead to EEG abnormalities and seizures, especially when administered without preoperative sedation and with controlled ventilation, rather than spontaneous breathing.

Nitrous Oxide

There are no human trials examining the effects of nitrous oxide in young children on neuronal structure and neurocognitive performance. Case studies in neonates after exposure to nitrous oxide *in utero* during the third trimester of pregnancy[67] or during cesarean delivery[64] indicated at least transient neurological sequelae, such as increased muscle tone, habituation to sound, resistance to cuddle, and fewer smiles,[67] without long-term follow-up.

In animal studies, no significant increase in apoptotic neurodegeneration was found in neonatal rats treated with 50%, 75%, or 150% (in a hyperbaric chamber) nitrous oxide for 6 h.[77] Another group of researchers also observed no increase in the apoptotic marker caspase 3 in neonatal rats exposed to 75% nitrous oxide for 6 h.[121] However, nitrous oxide at a dose of 75% exacerbated neuroapoptosis caused by 0.75% isoflurane.

Interestingly, similarly to some of the volatile anesthetics, nitrous oxide has been shown to protect from excitotoxic neurodegeneration.[146]

Xenon

Xenon's effects on neuronal structure and neurocognitive performance have not been studied in young children.

In animals, one study observed that a 6 h exposure to 0.5 MAC xenon did not increase apoptotic neuronal death in neonatal rats, but rather attenuated the neurotoxic effects of isoflurane and nitrous oxide.[121] Moreover, in the same study, xenon did not increase neuronal degeneration in organotypic hippocampal slices obtained from neonatal mice. No data on long-term neurocognitive function after neonatal exposure are available for xenon.

Withholding Anesthesia

Several studies in neonatal animals have documented the deleterious effects of painful stimuli or stress on increasing stress hormone levels, neuronal

cell death, pain thresholds, and abnormal behavior.[147–149] A recent study in neonatal rats has shown that ketamine anesthesia during painful injections ameliorated the deleterious effects of painful stimulation, without causing neurodegenerative effects.[91] It seems therefore conceivable that the deleterious effects of painful stimulation, such as during surgery, are abolished by anesthetics, whereas the painful stimulus, in turn, prevents the toxic effects of the anesthetics.

Mechanism of Anesthesia-Induced Neurotoxicity

Mechanism and selectivity of anesthesia-induced neurodegeneration are actively being investigated. It has been suggested that anesthesia-induced $GABA_A$-receptor activation and NMDA-receptor blockade during a critical stage in brain development lead to depression of neuronal activity, which initiates the apoptotic cell death cascade in immature neurons.[25] This hypothesis, however, has yet to be tested. Interestingly, contrary to this hypothesis, $GABA_A$ receptor stimulation leads to neuronal depolarization and not to decreased activity in immature neurons.[150]

Animal studies have demonstrated that anesthetic exposure is associated with a decrease in brain-derived neurotrophic factor,[120] a nonspecific protein supporting neuronal survival, growth, and differentiation, which is decreased during stressful states. The involvement of the intrinsic and the extrinsic pathways of the apoptotic cell death cascade have been demonstrated during anesthesia-induced neurodegeneration in rats.[126] However, the cellular mechanism for activation of the apoptotic cascade and the cellular selectivity remain unresolved. Apoptosis and neuronal cell death are integral parts of normal mammalian brain development. During normal fetal and neonatal brain development, neurons are produced in excess and as much as 50%–70% of neurons and progenitor cells undergo apoptotic cell death.[14–19] Apoptotic cell death is imperative to establish the normal structure of the CNS, and experimental disruption of the physiological apoptotic cell death mechanism will lead to intrauterine brain malformation and premature demise of the embryo.[20] Because the mechanism of anesthesia-induced neuronal cell death in not entirely understood, it remains unclear whether anesthesia induces apoptosis of cells not otherwise destined to die (i.e., pathological apoptosis), or whether it accelerates apoptosis of cells destined to die at a later time (i.e., premature physiological apoptosis).

Protective Adjuvants and Alternative Anesthetics

Several adjuvants, such as estradiol, pilocarpine, melatonin, and dexmedetomidine, have been identified in animal studies to ameliorate anesthesia-induced neurodegeneration.[83,122,130] However, their use in neonatal anesthesia has not been studied. The rarely used NMDA-antagonist xenon has been shown to be devoid of neurodegenerative properties in neonatal rats during a 6 h administration of 0.5 MAC and also to ameliorate isoflurane-induced neurodegeneration.[121] However, xenon is not widely available for clinical anesthesia practice. Preliminary data in guinea pigs and piglets have illustrated a significantly lower number of dying neurons after a fentanyl-based anesthetic, compared with isoflurane anesthesia.[123,124] While this regimen is similar to anesthetic management in critically ill premature neonates and during cardiac surgery, during "routine" pediatric practice, fentanyl is usually combined with a "neurotoxic" anesthetic, such as isoflurane, midazolam, or propofol.

Period of Susceptibility to Anesthesia-Induced Neurotoxicity

Preclinical studies strongly suggest a narrow window of susceptibility to anesthesia-induced neurodegeneration. The developing animal brain is particularly vulnerable to neuronal cell death after anesthetic exposure at 7-days-of-age in rodents and before 5-days-of-age in rhesus monkeys. However, vulnerability quickly diminishes with increasing age. It is therefore critical to understand the equivalent brain maturational state during human brain development. Estimates for the equivalent time period in humans have ranged from the third trimester of gestation to 3-yr-of-age, potentially rendering neonates, infants, and toddlers vulnerable to anesthesia-induced neurotoxicity. However, recent work suggests the equivalent period during human brain development to be closer to 17–20 wk of gestation, which would render the most commonly used animal models irrelevant for common pediatric anesthesia practice.[151,152]

In conclusion, apoptotic neuronal degeneration occurs naturally in up to 70% of neurons and progenitor cells during normal mammalian brain development, which extends over weeks in small rodents and over years in humans. This cell death process is critical to achieve normal brain morphology. A dramatic, brief increase in this natural apoptotic cell death has been observed in developing animal brains after exposure to every commonly used anesthetic studied thus far. However, at least for injectable anesthetics, doses administered in animal models are several times higher than comparable doses in pediatric anesthesia. Therefore, in order for the animal models to be applicable for clinical anesthesia practice, both the neurodegenerative effects and the anesthetic effects need to act by similar mechanisms, which have yet to be established. Volatile anesthetic doses, on the other hand, are comparable to clinical anesthesia practice. Thus, repeated evidence for clinical doses of isoflurane leading to a dramatic increase in neuronal apoptotic cell death in animal models raises serious concerns for pediatric anesthesia practice. The neurodegenerative effects of etomidate, desflurane, and sevoflurane have yet to be closely studied, whereas there is evidence from one study that the rarely used

anesthetic, xenon, in clinical doses does not have neurodegenerative effects and may be neuroprotective.

Even though neurodevelopmental outcome after anesthetic exposure during elective surgery in the neonatal period or infancy has not been studied in humans, anecdotal data suggest at least transient neurological impairment after prolonged exposure to several anesthetics. Moreover, several studies documenting long-term cognitive impairment after surgery and anesthesia in critically ill premature neonates and patients with congenital heart disease do not exclude a possible association of anesthetics with the observed dysfunction. Conversely, several anesthetics have demonstrated protective properties during ischemic insults to the developing brain. Therefore, given its dramatic implications for public health, anesthesia-induced neurotoxicity remains under intense study in animal models. Several animal studies have demonstrated anesthesia-induced neurodegeneration to be dose-dependent and exposure time-dependent. Moreover, animal data suggest neuronal cell death to be less severe after the administration of a single anesthetic versus a combination of several anesthetics. Laboratory studies indicate that a combination of a GABA-mimetic drug, such as a volatile anesthetic or propofol, and a NMDA antagonist, such as nitrous oxide or ketamine, might render the developing brain particularly susceptible to apoptotic neurodegeneration.

It remains unclear, however, whether anesthetics accelerate cell death in neurons destined to die due to natural apoptosis or if they trigger cell suicide in healthy neurons, which would have otherwise survived. If neurons are actively eliminated during anesthesia, it will be critical to demonstrate whether the developing brain is able to replace these neurons to maintain functional integrity. To answer these questions, it is imperative to study long-term neurocognitive function after neonatal anesthesia. However, long-term neurocognitive impairment has only been demonstrated in laboratory studies after neonatal administration of supraclinical doses of ketamine or propofol in mice or after prolonged isoflurane exposure in rats.[76,77,85] However, preliminary data in mice suggest that even a prolonged exposure to isoflurane as the single anesthetic does not alter behavior and neurocognitive function in adulthood.[153] These differential effects of anesthetics in two small rodent models mandate the examination of potential anesthetic neurotoxicants in several species, not only for their ability to trigger neuroapoptosis immediately after anesthetic exposure, but also in regards to long-term neurocognitive performance. Moreover, large animal and nonhuman primate studies should close the evolutionary gap between small rodents and humans.

Primum non nocere —Although prospective studies of neurodevelopment after elective surgery and anesthesia in infants are lacking, anecdotal data point to at least temporary neurological dysfunction after early life exposure to anesthetics. The implications of the possibility for neurotoxic effects of general anesthetics, as demonstrated in several animal models, mandate the vigilance of every anesthesiologist caring for young children. Because there are no commonly used anesthetics with proven safety records in animal studies, and because surgical procedures in neonates and infants are usually limited to those preserving life or quality of life, pediatric anesthesiologists should be vigilant to minimize the possibility of anesthesia-induced neurotoxicity in their youngest patients. Accordingly, meticulous care needs to be taken to prevent anesthetic overdoses and consideration should be given to formulate anesthetic plans involving regional anesthesia, where applicable, as well as avoiding the combined administration of multiple GABA-agonists and NMDA-antagonist anesthetics. However, hemodynamic stability and avoidance of hypoxia should still remain the principal objectives to prevent postoperative neurocognitive impairment. Moreover, pediatric anesthesiologists are encouraged to actively investigate this phenomenon in preclinical as well as clinical studies. The entire anesthesia community, the pharmaceutical industry, and government agencies are called upon to support research into the mechanism and prevention of anesthesia-induced neurodegeneration. The Food and Drug Administration has started this process by convening the Anesthesia and Life-Support Advisory Committee in March of 2007 (the transcript can be obtained at http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007–4285t1.pdf). At this point, the committee unanimously agreed, "there are not adequate data to extrapolate the animal findings to humans." The committee concluded, "the existing and well-understood risks of anesthesia" (hemodynamic and respiratory) "continue to be the overwhelming considerations in designing an anesthetic, and the understood risks of delaying surgery are the primary reasons to determine the timing."

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