Learning Objectives:

I. Are parents useful (in the operating room)?
   a. To discuss the developmental differences in child development
   b. To review the incidence of postanesthesia behavioral disturbances
   c. To determine the benefit of parental presence in the operating room

II. Will anesthesia make my child stupid?
   a. To determine the incidence of cognitive impairment following anesthesia in adults
   b. To review the animal data of neonatal neurotoxicity
   c. To review the human data of neonatal anesthesia exposure on learning disabilities

This lecture has a myriad of possible topics, but I have chosen to focus on 2 current issues

1. Anesthesia neurotoxicity in the developing brain: Do anesthetic agents make your child stupid
   a. To discuss the developmental differences in child development
   b. To review the incidence of postanesthesia behavioral disturbances
   c. To determine the benefit of parental presence in the operating room

2. Parental presence in the OR and premedication agents: Their role in pediatric anesthesia

1. ANESTHESIA NEUROTOXICITY IN THE DEVELOPING BRAIN: DO ANESTHETIC AGENTS MAKE YOUR CHILD STUPID

An area of intense interest in both the scientific community and lay press involves the findings of anesthetic associated toxicity in the developing central nervous system. Early work in the 1980s by Uemura and colleagues noted that rats exposed to varying concentrations of halothane from the time of conception to PND28 had a decrease in synaptic density and that these exposed animals also demonstrated behavioral disturbances (1). More recent investigations with newborn animal models have reported apoptosis in multiple areas of the central nervous system during this period of rapid synaptogenesis when these animals are exposed to drugs that work via N-methyl D aspartate antagonists (NMDA) or Gamma-aminobutyric acid (GABA) agonists (2-11). These findings have been reported in both rodent and non human primate models. Ketamine, sevoflurane and isoflurane have all been shown to have dose-dependent and time-exposure effects on neuroapoptosis in the developing brain. When these agents are combined, these drugs act synergistically with regards to both their anesthetic and neuroapoptotic effect. In addition to a dose effect, these animals have a period, or window of vulnerability, in which these agents act in the developing brain. This window of vulnerability differs among species, and though there are no specific studies on the vulnerability period in humans, these animal models suggest that the vulnerable period in humans correlate to a human period of late pregnancy to early childhood. Although the data is mixed with respect to the behavioral/neurocognitive outcomes in rodents, there is no data on the neurocognitive function following anesthetic exposures in the nonhuman primate.

To complicate the situation, rodent studies have shown that ketamine exposure during this period of rapid synaptogenesis can increase neuroapoptosis and alter behavior in exposed rat pups; however, if rat pups are exposed to chronic pain (in the absence of the drug), chronic pain can also cause an increase in neuroapoptosis. If these animals are exposed to chronic pain and ketamine, neuroapoptosis is markedly attenuated (12). Stratmann and colleagues have shown in rat pups that exposure to increased levels of carbon dioxide results in an increase in neuroapoptosis to a level that is similar to that observed with exposure to isoflurane. However, neurocognitive performance in the carbon dioxide exposed group was similar to control animals, while animals exposed to isoflurane had neurocognitive impairment (7). Stratman et al has challenged the view of neuroapoptosis and has suggested that anesthetic agents may effect neurogenesis. Recent animal work suggests that magnesium administration can cause neuroapoptosis (13). Thus, women receiving magnesium infusions to suppress labor or treat preeclampsia may create a risk factor for neurocognitive behavior disorders. How do these findings translate to the human experience? The answers are less clear. Two studies suggest a possible association with neurocognitive impairment and one does not. Wilder and others, looking at databases and county registries in the Rochester Minnesota area, suggest that exposure to anesthesia may have a detrimental effect with regards to learning disabilities. In this study, the investigators reported on a cohort of 5357 births in Rochester Minnesota between 1976 and 1982. The incidence of learning disabilities and its relationship to anesthetic exposure was determined while adjusting for other possibly relevant covariables (14). In this study, the authors concluded that 2 or more anesthetic exposures increased the odds of a learning disability. Though this paper has a significant number of strengths (sample size, inclusion of covariates, a wide range of surgical procedures, varying anesthetic exposures, no preconceived outcome results (i.e. no selection or
observational bias), there are a few limitations that raise caution in interpreting the results. Namely, the study population had anesthesia performed before pulse oximetry and end-tidal monitoring were standard of care or available. In addition, because of the retrospective nature of the study, learning disability evaluations may have been self-selective. Another study to suggest an association between anesthetic exposure and neurobehavioral outcome is the report of Kalkman and colleagues (15) on 249 children following exposure to anesthesia between 0-6 years of age during years 1987, 1991, 1993 and 1995). In a cross-sectional study, these investigators surveyed parents of children from the Netherlands who had undergone GU surgery with a questionnaire on behavioral development. The behavioral development measurement involved the Dutch translation of the Child Behavior Check List developed and validated in the United States. This test completed by the parents, reports their child’s competencies and behavior/emotional problems based on the child’s activities, social relations and school performance. The parents reported a higher trend in learning deficits. However, based on their findings, a cohort of over 6,000 patients would be needed to confirm or refute their findings.

However, in a study of twin cohorts from the Netherlands, Bartels and others reported no causal relationship between anesthesia and learning deficits. In their study of 1143 monozygotic twin pairs, Bartels noted that twins exposed to anesthesia before age 3 had significantly more cognitive problems and lower educational achievement scores than did twins not exposed to anesthesia. However, in twin pairs that were discordant for anesthesia (i.e. one twin exposed and one twin not exposed), these twins were not different from each other (16).

WHAT IS THE CLINICIAN TO DO WITH ALL THIS INFORMATION??

At this time, no studies demonstrate that anesthetic drugs cause harmful effects to the nervous systems of children. There is no phenotype for this anesthetic-associated neurocognitive disorder. The retrospective studies to date suggest that multiple exposures might entail risk. However, these studies suffer from all the weaknesses inherent in retrospective designs. Specifically, they cannot control for the multiple confounding variables that exist with normal growth and development. However, the existing scant human data and the clinical impression all suggest that anesthetic exposures up to several hours are not associated with risk. This is similar to the findings in animal models. The bottom line for the practicing anesthesiologist, and concerned parents, is that at present there is no direct evidence that exposure to anesthetic drugs, per se, is unsafe for children. Of course, there are real risks of anesthesia in children, including hypoxia and cardiovascular compromise. The available data suggest that discussions about anesthetic risks in young children continue to focus primarily on the very real risks of airway compromise, hypoxia, and cardiovascular instability, and not on the hypothetical risk of neurologic injury from anesthetic drugs. The present data do not support postponing necessary surgery in children until a later age to avoid hypothetical dangers of exposure to anesthetic drugs.

2. PARENTAL PRESENCE IN THE OR AND PREMEDICATION AGENTS: THEIR ROLE IN PEDIATRIC ANESTHESIA

This aspect of the lecture will focus on premedication and the induction of pediatric patients presenting for surgery. In order to better assess the role of premedications and induction techniques, it is imperative to understand the psychological needs of children and how they differ during development. Also important in this process of preparing children and their parents for surgery is to understand what the risk factors are for both patient and parent with regard to preoperative anxiety (18-23). The role of premedications and induction techniques are truly dependent on the perioperative environment and the philosophy of the institution. The endpoints of success to reduce preoperative anxiety need to be defined. Mask acceptance and ease of induction are classically measured, but in fact may be surrogate endpoints. Postoperative behavioral changes may be more significant findings, but postoperative behavioral changes may also be related to other factors in the child’s hospitalization/care. Studies have shown that 54% of children undergoing outpatient surgery exhibit postoperative behavioral changes (24-27). These changes include nightmares, disruptive sleep, enuresis, separation anxiety and temper tantrums. Though difficult to assess, the incidence of preoperative anxiety in children is estimated to be up to 75%. Anxiety is that feeling of tension, nervousness and worry associated with increased autonomic nervous system activity. Age-related concerns involve stranger anxiety, parental separation, pain discomfort, disfigurement, and loss of control, fear of awareness, fear of not waking up and fear of being put to sleep. Risk factors for increased preoperative anxiety in children include age (coping strategies), children with high trait anxiety, shyness, inhibited temperament and increased parental anxieties. In the US, the three most common interventions for children with preoperative anxieties include:

1. Preoperative preparation programs
2. Parental presence at induction of anesthesia
3. Preanesthetic medication

PREOPERATIVE PREPARATION

Most studies have suggested that preoperative preparation programs reduce anxiety and enhance coping in children. Institutional programs have
evolved to include play therapy, music therapy, child-life preparation and the teaching of coping skills (28-30).

**PARENTAL PRESENCE**

Parental presence at induction of anesthesia has increased in frequency (31). The advantages of parental presence include the decreased need for premedications and avoidance of separation anxiety. Concerns regarding parental safety, effectiveness, the child's well being, increased parental anxiety, and consequently, increased patient anxiety, have been cited as the down side to parental presence (31-36). When parental presence is compared to the use of oral midazolam, children who were premicated with oral midazolam had less anxiety than the children in the parental presence group. In addition, in studies of children where parental presence is combined with oral midazolam and compared to children who only received oral midazolam, there was no further reduction in patient anxiety.

**PREANESTHETIC MEDICATION**

Which agent is best and through which orifice it should be administered have been the subjects of numerous papers in the history of pediatric anesthesia. The various drugs, routes of administration, and dosages are well reviewed in the textbooks of pediatric anesthesia (Krane & Davis, Chapt 8, Smith’s Anesthesia for Infants and Children, 8th edition) (20). In the past, most preanesthetic medications have been dictated by tradition. However, more recently, Kain has reported that sedative premedications were used in approximately 50% of all children and adults undergoing surgery, and that in children, midazolam was the most commonly used premedication (>96%) followed by fentanyl and ketamine. For purposes of discussion, the agents midazolam, OTFC, and the -2 agonists clonidine and dexmedetomidine will be reviewed (36-44).

Recently, the use of -2 agonists has come into wider use in pediatric anesthesia. The use of clonidine has been well studied, and more recently the role of dexmedetomidine is being evaluated. Dexmedetomidine bioavailability following per oral, buccal and intramuscular administration were 16, 82 and 104% respectively (42). Studies in adults by Yuen et al. using crossover design have shown that nasal administration of dexmedetomidine has a peak sedative effect in 90-105 minutes and significant sedation occurring in 45-60 minutes. In addition, 75% and 92% of adult volunteers receiving 1.0 and 1.5 µg/kg respectively had OAA/S scores of 3 or less. In a blinded study involving children premedicated with both oral midazolam (0.5 mg/kg), nasal dexmedetomidine (0.5 µg/kg) or nasal dexmedetomidine (1.0 µg/kg), Yuen et al. noted that intranasal dexmedetomidine produced more sedation than midazolam, but patient cooperation at the time of induction was similar to the group receiving midazolam (43,44)

**REFERENCES:**


