PREMEDICATION OF THE CHILD UNDERGOING SURGERY

C. ABDALLAH[*] AND R. HANNALLAH[**]

The preoperative period is a stressful event for the majority of individuals undergoing surgery. This is especially true in the pediatric patient and is related to a limited understanding of the nature of the illness and the need of surgery by young children. Pharmacological and behavioral interventions are used to treat preoperative anxiety in children and their parents.

Among the different results that may be achieved with premedication such as amnesia, optimization of preoperative conditions and prevention of physiological stress, the primary aim in children is anxiolysis. Almost 50% of children show signs of significant preoperative fear and anxiety[1]. It has been reported that there are correlations between heart rate, blood pressure, and behavioral ratings of anxiety[2]. In order to alleviate physiological and psychological effects of preoperative anxiety in children, most anesthesiologists use either parental presence or sedative premedication, since separation from parents and induction of anesthesia are considered the most perioperative stress inducing phases. Both approaches are considered appropriate choice of interventions. Anesthesiologists who allow parental presence during induction of anesthesia use sedative premedication least frequently, and vice versa[3,4].

Historically, it is interesting to document that the initiation of the practice of pediatric outpatient surgery was associated with major modifications such as discontinuation of the use of preoperative sedation in this patient population. This was thought to be necessary because the most popular premedicant drugs available at the time were long acting (e.g., morphine and Nembutal), delayed recovery, and increased the incidence of postoperative vomiting. In addition, there was no available oral premedication agent. This practice resulted in compromising the psychological welfare of many children for the sake of efficiency and rapid discharge. Availability of oral midazolam premedication is the main reason pharmacological sedation regained popularity in pediatric anesthesia, especially in ambulatory practice.

Parental Presence or Premedication?

Early studies suggested reduced anxiety and improved patient cooperation if parents were present during induction[5,6]. The majority of parents prefer to be present during induction of anesthesia regardless of the child's age or previous surgical experience[7], and also regardless of their experience with prior parental presence or premedication of their child in the case of repeated surgery[8].

Concerns regarding parental presence on induction of anesthesia include a negative behavioral response to stress in some children when a parent is present and an upsetting experience to the parents, especially if watching their child going limp or when leaving their child after induction[9-10]. This has been demonstrated by an increase in heart rate and skin conductance levels in mothers[11]. Oral midazolam has been shown to be more

* Associate Professor.
** Professor, Anesthesia Division, Children's National Medical Center, Washington DC. 20010.
   Corresponding author: Claude Abdallah, MD, Division of Anesthesiology, Children's National Medical Center, 111 Michigan Avenue, N.W, Washington, DC 20010. Tel: (202) 476-2025, E-mail: cabdalla@childrensnational.org

effective in reducing a child's anxiety than parental presence and parental presence combined with oral midazolam was not superior in reducing a child's anxiety than sedation alone[12]. It has been shown that parental presence during induction of anesthesia is mostly beneficial in children older than 4 years of age who share a "calm" baseline personality with the accompanying parent[13,14]. Limitations to these controlled studies may be that randomization in subject recruitments may not reflect the everyday practice of anesthesiologists who carry an individual approach in dealing with their patients and parents.

If parental presence during induction is deemed to be in the child's best interest, a clear explanation that describes what the parent can expect to happen during the periinduction period can significantly decrease parental anxiety and increase their satisfaction, which may be reflected in the child's behavior[15-17]. Predictive risk factors for children who would probably benefit from sedative premedication include children between the ages of 2 and 6 years, who are shy and inhibited, those who have a history of prior stressful medical encounters and those accompanied by an anxious parent[18,19]. In the extremely anxious child, premedication would be indicated in order to avoid a traumatic anesthetic induction, with the possibility of postoperative psychological disturbances[20].

Premedication

The major objectives of preanesthetic medication are to decrease the stress response with preservation of hemodynamic parameters, facilitate anesthesia induction and produce amnesia. The child's age, body weight, drug history, allergic status and underlying medical or surgical conditions are factors to be taken into consideration prior to administration of premedication. In most cases, medications administered without a needle are more pleasant for children, the family and the care team. Oral premedication does not increase the risk of aspiration pneumonia[21].

Different medications may be used for premedication.

Benzodiazepines

Midazolam: The most commonly used sedative premedicant in the preoperative holding area is midazolam[22]. It should be administered under direct supervision with the patient placed in a closely monitored bed space in the preoperative holding area. Major attributes of midazolam are its availability as an oral preparation and its short onset and offset of action. As a standard syrup preparation, it exists in both an open and closed ring structure, the proportion of which is pH dependent. At lower pH values there is a greater proportion of drug in the open ring and at higher pH values there is a reduction in the proportion of the drug in the open ring configuration. Since only the open ring formulation is lypophilic and physiologically active, bioavailability is highly sensitive to changes in pH. Therefore, the combination of any "home made" diluents with the intravenous midazolam formulation could significantly alter both the absorption rate and the bioavailability[23]. The most common oral dose used is 0.5 mg/kg and ranges from 0.25 to 0.75-1 mg/kg have been described. Higher doses of midazolam (1 mg/kg) appear not to offer any additional benefits, and may cause more side effects. Commercially prepared midazolam formulation is rapidly absorbed with patients demonstrating a satisfactory degree of sedation and anxiolysis within 10 minutes of consumption with a higher percentage at 20 minutes. A bitter taste has been described after oral and nasal administration. The dose of oral midazolam should be adjusted in children taking depressants or inducers of the cytochrome oxidase system,

such as anticonvulsants or barbiturates.

Other routes of administration of midazolam are used; these are the nasal, rectal, intramuscular and intravenous routes. The dose of midazolam is 0.025 to 0.1 mg/kg intravenously. The bioavailability [and suggested dose] of midazolam is 0.9 [0.1 to 0.2 mg/kg] after intramuscular injection, 0.57 [0.2 mg/kg] after intranasal, 0.4 to 0.5 [1 mg/kg] after rectal, and 0.3 [0.25 to 0.75 mg/kg] after oral administration. A sublingual route of administration [0.2 mg/kg] has also been described[24-30].

After intravenous administration of midazolam, the time to peak central nervous system (CNS) electroencephalographic effect is 4.8 minutes. It is preferable to wait this interval of time prior to administering an additional dose of midazolam in order to avoid over sedation. Intravenous midazolam is best reserved for children who already have a functioning IV line to avoid the added trauma of venipuncture.

Peak plasma concentrations of midazolam after intranasal administration occurs in only 10 minutes, however, discomfort has been associated to this route secondary to irritation. Also, a preservative-free midazolam is recommended when using this route of administration since intranasal midazolam with preservative has been shown to have neurotoxic effects in an animal model[31].

There is synergism between propofol and midazolam on γ-aminobutyric acid (GABA) receptors[32]. Oral midazolam decrease the infusion requirements of propofol by a third during a propofol-based anesthetic[33]. After premedication with oral midazolam (0.5 mg/kg), in children 1 to 3 years of age post adenoidectomy, emergence and early recovery were delayed with no change in discharge times after induction of anesthesia with propofol, and maintenance with sevoflurane[34]. Spontaneous eye opening and discharge time were delayed as compared with placebo after 25 minutes of sevoflurane anesthesia[35]. However, extubation, awakening and discharge times were not affected after sevoflurane anesthesia in children 1 to 10 years receiving the same dose of oral midazolam[36].

Midazolam has the advantage of producing anterograde amnesia. Memory usually becomes impaired within 10 minutes after oral midazolam[37]. This has a beneficial effect in children requiring repetitive interventions.

Midazolam, like other benzodiazepines increases the threshold for central nervous system toxicity with seizures; however the threshold for cardiovascular toxicity is unchanged. Thus, after premedication with midazolam or a benzodiazepine, cardiovascular collapse after regional anesthesia toxicity may occur unassociated with CNS symptoms of toxicity.

Secondary and adverse effects to midazolam may include a paradoxical effect with behavioral changes and agitation and hiccups. This may occur independently of the mode of administration, i.e. rectal, nasal, or oral ketamine, 0.5 mg/kg, IV has been shown to reverse the agitation[38].

Lorazepam: may be administered orally, intravenously, or intramuscularly and is metabolized by the liver to inactive metabolites. The intravenous formulation has been reported to be neurotoxic in neonates[39]. Lorazepam has a slow onset and offset of action, and therefore is better used for inpatients. It has good amnestic properties and less tissue irritation than diazepam. The usual dose is 0.05 mg/kg administered orally or intravenously to older children; however a dose of 0.025 mg/kg has been adequate to decrease preoperative anxiety[40].

Diazepam: has a greater fat solubility than midazolam and a faster CNS effect after intravenous administration (1.6 min); however it is metabolized to desmethyldiazepam with a pharmacologic activity equal to the parent compound[41]. Diazepam is an unpopular choice as a preoperative premedicant in young children

because of immature liver function that would lead to a prolonged half life. The average oral dose for premedicating healthy children with diazepam ranges from 0.1 to 0.3 mg/kg. When administered rectally, diazepam appears to be less effective than rectal midazolam[42]. The intramuscular route is not recommended because it is painful and absorption is erratic[43].

Barbiturates

Not commonly used for premedication in children since the availability of short acting benzodiazepines. A major disadvantage is hyperalgesia which can induce agitation in children with pain. Intravenous methohexital has a relatively shorter elimination half-life (3.9 ± 2.1 hours) than thiopental (9 ± 1.6 hours) because of a faster hepatic metabolism[44]. Methohexital, in a rectal dose of 20 to 30 mg/kg, may result in sleep/sedation in 15-20 min but at the risk of producing hiccups, apnea, airway obstruction, laryngospasm, seizures, in addition to an unpredictable systemic absorption and possible allergic reaction[45,46]. An increase in absorption because of rectal mucosa abnormality may lead to cardio-respiratory arrest. Contraindications to methohexital include porphyria, hypersensitivity and temporal lobe epilepsy[47]. The dose of rectal thiopental and onset of action are similar to methohexital[48].

Nonbarbiturate Sedative

Chloral hydrate is an orally administered nonbarbiturate (20 to 75 mg/kg with a total maximum dose of 2 g). It is devoid of analgesic properties and has a bitter taste. Its principal advantage is that it can be administered orally or rectally with a relatively good sedation within 30 to 45 minutes. Its use is less frequent than midazolam as a premedicant because of its slow onset and long elimination half-life. Its use is not recommended in neonates and patients with liver disease because of impaired metabolism, and the potential accumulation of toxic metabolites leading to metabolic acidosis, renal failure, and hypotonia[49]. The active metabolite of chloral hydrate, trichloroethanol, has a long half life in toddlers and in preterm infants (39.8 ± 14.3 hours). Therefore, there is a risk for residual drug effect and prolonged sedation or re-sedation[50]. Airway obstruction may occur in children with enlarged tonsils[51]. Deaths after chloral hydrate sedation have been reported[52]. Concerns for potential carcinogenicity with chronic administration exist as well as irritation of the skin, mucous membranes, and gastrointestinal tract, possibly in relation to its metabolism to trichloroacetic acid.

Phenothiazines

Promethazine (0.25 to 0.5 mg/kg intravenously, intramuscularly, or orally) has the advantage to possess several beneficial effects such as being an antihistaminic (H_1 blocker), an antiemetic, anti-motion sickness, and an anticholinergic in addition to being a sedative. However, it is not a popular premedicant drug in pediatric ambulatory anesthesia because of dystonic reactions reported with its use and because of its long elimination half-life (8 to 12 hours) and an insufficient effect when prescribed alone.

Ketamine

Is a phencyclidine derivative that antagonizes the N-methyl-D-aspartate (NMDA) receptor. The principal action of ketamine is due to the central dissociation of the cortex from the limbic system, providing good sedation and analgesia while preserving upper airway muscular tone and respiratory drive. Ketamine also relaxes the smooth musculature of the airway stimulated by histamine and has its application in case of potential risk for bronchoconstriction. It is recommended to administer an antisialagogue (atropine, glycopyrrolate) with ketamine in order to decrease the amount of oral secretions that may occur and to decrease the risk of laryngospasm. Hallucinations during recovery from ketamine may occur mostly in older children although oral ketamine has been reported to reduce emergence delirium. Co-administration of benzodiazepines or subsequent administration of general anesthetic agents reduces the incidence of hallucinations to approximately 4%[53]. Recovery of patients who have received ketamine in a quiet environment with the least stimulation helps decrease the incidence of undesirable effects such as hallucinations, nightmares, and delirium. The most common adverse reaction to ketamine is postoperative vomiting, which occurs in 33% of children[54]. The dextro-isomer of ketamine has more potent analgesia and reduced incidence of side effects[55].

Intravenous ketamine has a fast onset of effect (<1 min.). Duration of action of a single IV dose is 5 to 8 minutes (α-elimination half-life of 11 minutes and a β-elimination half-life of 2.5 to 3.0 hours)[56]. Ketamine is administered in very low doses intravenously (0.25-0.5 mg/kg) or intramuscularly (1-2 mg/kg) either alone or preferably in combination with low-dose midazolam (0.05 mg/kg) along with atropine (0.02 mg/kg) for sedation. The dose of ketamine needed to prevent gross movement in infants younger than 6 months of age is four times greater than in children 6 years of age[57]. Bioavailability of ketamine is approximately 93% after intramuscular administration. The intramuscular route of administration is very useful for children who are uncooperative, refuse oral sedation and become combative. These children become adequately calm in around 3 minutes and accept a mask inhalation induction of anesthesia. There is no documentation of prolongation of the hospital discharge times after IM ketamine administration (2 mg/kg) even after brief surgical procedures and a minimal likelihood of delirium or bad dreams during recovery[58]. However, the combination of intramuscular ketamine (2 mg/kg) and midazolam (0.1 to 0.2 mg/kg) may prolong recovery and discharge times after brief ambulatory procedures[59]. A larger dose (4 to 5 mg/kg) sedates children within 2 to 4 minutes, and a dose of 10 mg/kg usually produces deep sedation. Larger and repeated doses are associated with hallucinations, nightmares, vomiting, and a prolonged recovery from anesthesia. Acute tolerance to ketamine has been reported.

Ketamine has also been administered also via oral, nasal, and rectal routes. After oral administration and nasal administration, bioavailability is 17% and 50% respectively.

Oral ketamine alone and in combination with midazolam has been used for premedication in healthy children and those with congenital heart defects. Sedation is usually achieved after a dose of 5 to 6 mg/kg of oral ketamine in most children within 12 minutes, the depth of sedation is sufficient to obtain intravenous access in more than half of the children. Larger doses may prolong recovery from anesthesia. The combination of oral midazolam and ketamine is synergistic in its efficiency for preoperative sedation. The combination of oral ketamine (3 mg/kg) and midazolam (0.5 mg/kg) does not seem to prolong recovery time for procedures longer than 30 minutes[60].

Nasal transmucosal ketamine at a dose of 6 mg/kg is also effective in sedating children within 20 to 40 minutes before induction of anesthesia. Only preservative free ketamine should be given nasally to avoid neurotoxicity, the 100 mg/ml concentration is preferable to minimize the volume administered in the nose[61].

Rectal ketamine administration has a bioavailability of 25% and can result in an unpredictable effect.

Rectal ketamine (5 mg/kg) produces usually anxiolysis and sedation within 30 minutes of administration[62].

It is of note that ketamine may produce increases in intracranial pressure (ICP) as a result of cerebral vasodilatation, it also increases $CMRO_2$; therefore its administration should be avoided in children with intracranial hypertension. Administration of ketamine also may not be of choice in any child with a history of psychiatric or seizure disorder because of its psychotropic and epileptogenic effects. Ketamine may be potentially dangerous in the presence of eye trauma since increase in intraocular pressure has been documented with its use.

Studies in mice and rats have correlated ketamine treatment with increased neuronal apoptosis during rapid synaptogenesis after birth. The clinical importance of these findings to humans is unclear.

Opioids

Opioids may be used as a preanesthetic medication to children with preoperative pain; however opioid-related side effects such as respiratory depression, dysphoria, pruritus and nausea/vomiting are to be taken into account when administering opioids. If opioids are used in combination with other sedatives such as benzodiazepines, the dose of each drug should be appropriately adjusted to avoid serious respiratory depression.

Neonates are very sensitive to the respiratory depressant effects of opioids, and they are rarely used to premedicate this age group.

Fentanyl may be administered by parenteral, transdermal, nasal, and oral routes. A "lollipop" delivery system, oral transmucosal fentanyl citrate (OTCF) is more accepted by children than other routes as a premedicant. Fentanyl is strongly lipophilic, and is readily absorbed from the buccal mucosa with an overall bioavailability of approximately 30-50%[63]. The optimal dose as a preanesthetic medication with minimal desaturation and preoperative nausea appears to be 10 to 15 μg/kg. Children begin to show signs of sedation within 10 minutes after receiving this dose. Recovery from anesthesia after a premedication of 10 to 15 μg/kg of oral fentanyl is similar to that after 2 μg/kg intravenously. Doses greater than 15 μg/kg are not recommended because of opioid side effects, particularly occasional respiratory depression. The incidence of the opioid associated side effects is increased when the interval between completion of "lollipop" and induction of anesthesia is prolonged[64,65]. OTFC is now primarily indicated for the treatment of breakthrough cancer pain. Fentanyl has also been administered nasally (1 to 2 μg/kg) but primarily after induction of anesthesia as a means of providing analgesia in children without intravenous access.

Sufentanil is 10 times more potent than fentanyl. Several instances of reduced chest wall compliance have been reported in children after nasal sufentanil, as well as a higher incidence of nausea and vomiting and a prolonged discharge time when compared to nasally administered midazolam[66]. These potential side effects and prolonged hospital stay after nasal sufentanil makes it an unpopular choice for premedication.

Morphine sulfate may be administered intramuscularly (0.1 to 0.2 mg/kg) or intravenously (0.05 to 0.1 mg/kg) or orally. Absorption may not be adequate when given rectally.

Meperidine is a synthetic opioid with a more rapid onset of action and reduced duration of action than morphine. The usual dose for premedication in children is 1 to 2 mg/kg intramuscularly 1 hour before induction. Meperidine may also be administered intravenously and orally. An oral dose of 1.5 mg/kg may be used to sedate patients before anesthesia. Meperidine is metabolized to normeperidine and central nervous

system excitation (seizures, twitches and tremor) may result from accumulation of normeperidine after chronic or large doses administration[67].

Tramadol is a weak µ-opioid receptor agonist whose analgesic effect is mediated via inhibition of norepinephrine reuptake and stimulation of serotonin release. Intravenous tramadol (1.5 mg/kg) given before induction of general anesthesia has been as effective as local infiltration of 0.5% bupivacaine (0.25 ml/kg) for ilioinguinal and iliohypogastric nerve blocks for pain control, but associated with a higher incidence of nausea and vomiting[68].

Butorphanol is a synthetic opioid agonist-antagonist with properties similar to those of morphine that can be administered nasally. A dose of 0.025 mg/kg administered nasally immediately after the induction of anesthesia was shown to provide good analgesia after myringotomy and tube placement at the expense of increased incidence of emesis at home compared with children who received nonopioid analgesics such as acetaminophen[69].

Codeine is a commonly prescribed oral opioid, which must undergo O-demethylation in the liver to produce morphine to provide effective analgesia. Five to 10 percent of children lack the cytochrome isoenzyme (CYP450 2D6) required for this conversion and therefore do not derive analgesic benefit. Codeine can be given orally or intramuscularly but should not be administered intravenously because of the risk of seizures. The usual oral dose of oral codeine is 0.5 to 1.5 mg/kg with an onset of action within 20 minutes and peak effects between 1 to 2 hours. Codeine has an elimination half-life of 2.5 to 3 hours. The combination of codeine with acetaminophen is effective in relieving mild to moderate pain.

α₂ Agonists

Clonidine, an α₂ agonist, causes dose-related sedation by its effect in the locus ceruleus through its inhibition of adenylate cyclase. The plasma concentration peaks at 60 to 90 minutes after oral administration and at 50 minutes after rectal administration[70]. The need to administer clonidine 60 minutes before induction of anesthesia makes its use impractical in most clinical settings. An oral dose of 3 µg/kg given 45 to 120 minutes before the surgery produces comparable sedation to that of diazepam or midazolam[71]. Clonidine acts both centrally and peripherally to reduce blood pressure and therefore it attenuates the hemodynamic response to intubation. It is usually administered in combination with atropine. In children undergoing tonsillectomy, the group who received oral clonidine, 4 µg/kg, showed more intense anxiety on separation and during induction than the group who received midazolam (0.5 mg/kg) with reduced mean intraoperative blood pressures, reduced duration of surgery, anesthesia, and emergence, and decreased need for supplemental oxygen during recovery but greater postoperative opioid requirements, greater pain scores, and excitement in the clonidine group. Time to discharge, postoperative nausea/vomiting, and 24-hour analgesic requirements were similar in both groups[72].

Antihistamines

Not commonly used because their sedative effects are variable. Diphenhydramine is an H₁ blocker with mild sedative and antimuscarinic effects. The dosage for children is 0.5 mg/kg intravenously, or intramuscularly[73]. Although the duration of action is 4 to 6 hours, it does not appear to interfere with recovery

from anesthesia.

Hydroxyzine has antiemetic, antihistaminic, and antispasmodic effects with minimal respiratory and circulatory changes. It is usually administered IM at a dose of 0.5 to 1.0 mg/kg.

Anticholinergic Drugs

Anticholinergic agents were commonly used in the past to prevent the undesirable bradycardia associated with some anesthetic agents (halothane and succinylcholine), to minimize the autonomic vagal reflexes, and to reduce secretions. Current inhalational anesthetics are not associated with bradycardia and do not stimulate salivary or tracheobronchial secretions, therefore, the routine use of an anticholinergic drug is not generally needed. In the majority of cases, anticholinergics are given after intravenous access is established.

Atropine (0.02 mg/kg) and scopolamine (0.01 mg/kg) both have CNS effects, although the sedating effect of scopolamine is 5 to 15 times greater than atropine. Atropine is more commonly used and is a better vagolytic agent than scopolamine, whereas scopolamine is a better sedative, antisialagogue, and amnestic. Glycopyrrolate is the only agent that does not cross the blood-brain barrier, so it does not cause confusion. When compared to atropine, it is less effective in attenuating bradycardia during induction. The central sedative effects of both atropine and scopolamine may be antagonized with physostigmine. Preoperative administration of oral atropine or oral glycopyrrolate does not alter the incidence or degree of hypotension during induction of anesthesia.

Anticholinergic agents are very useful as an adjuvant to ketamine anesthesia because of their antisialagogue and central sedative effects.

The recommended doses of anticholinergics are scopolamine, 0.005 to 0.010 mg/kg, atropine, 0.01 to 0.02 mg/kg and glycopyrrolate 0.01 mg/kg IV, IM.

Topical Anesthetics

Topical anesthetic creams may represent an attractive alternative to intradermal infiltration, but sometimes with some limitations.

EMLA cream (eutectic mixture of local anesthetic, Astra Zeneca, Wilmington, DE) is a mixture of two local anesthetics (2.5% lidocaine and 2.5% prilocaine). One-hour application of EMLA cream to intact skin with an occlusive dressing provides adequate topical anesthesia for an intravenous catheter insertion. However, EMLA causes venoconstriction and skin blanching, making intravenous cannulation more difficult. Methemoglobinemia may occur secondary to prilocaine[74]. However, a 1-hour application of EMLA cream and a maximum dose of 1 g did not induce methemoglobinemia when applied to intact skin of full-term neonates younger than 3 months of age[75].

Ametop is a topical local anesthetic (4% tetracaine) with onset time of 30- to 40-minute. The advantages are the absence of venoconstriction or skin blanching, and there is no risk of methemoglobinemia.

ELA-Max (4% lidocaine) decreases pain associated with intravenous catheter insertion after only a 30-minute application. In addition, ELA-Max blanches the skin to a lesser extent and dilates veins better than EMLA cream. There is no risk of methemoglobinemia with this formulation.

The S-Caine Patch (ZARS, Inc., Salt Lake City, UT), is a eutectic mixture of lidocaine and tetracaine (70

mg of each per patch) that uses a controlled heating system to accelerate delivery and analgesic effect of the local anesthetic. An application time of 20 minutes lessens pain associated with venipuncture in children and is associated with only mild and transient local erythema and edema and no skin blanching[76]. Methemoglobinemia has not been reported with this formulation..

Lidocaine iontophoresis uses an impregnated electrode, current generator, and a return pad to carry ionized lidocaine through the stratum corneum[77]. It provides similar pain relief for insertion of intravenous catheters in children as EMLA cream but requires training and equipment for application[78]. It may cause a stinging pain during current application and potential skin burns from the electrodes[79].

In summary, the primary goal of premedictaion in children is to ease the induction of anesthesia by facilitating a smooth separation from the parents. Other pharmacological effects (amnesia, prevention of physiologic stress, reduction of total anesthetic requirements, decrease risk of aspiration, of acidic stomach content, and analgesia) may also be achieved. Special considerations for patients with deteriorating mental status, with airway obstruction or patients with hemodynamic instability/intolerance to hypercapnia (such as those with significant increases in pulmonary artery pressure/pulmonary arteriolar resistance) or with systemic organ failure should be taken into account prior to administration of premedication. In these cases, parental presence may be the preferable choice. The major effect of premedication is to allay anxiety, but has the potential to produce sedation and should always be administered with caution under supervision and close monitoring. Tools for administration of supplemental oxygen, ventilation support and resuscitation should be readily available.

References

1. KAIN ZN, CALDWELL-ANDREWS AA: Preoperative psychological preparation of the child for surgery: an update. *Anesthesiol Clin North Am*; 2005, 23:597-614.
2. WILLIAMS JGL: Psyphysiological responses to anesthesia and operation. *JAMA;* 1968, 203:127-129.
3. KAIN ZN, MAYES LC, BELL C, ET AL: Premedication in the United States: a status report. *Anesth Analg;* 1997, 84:427-432.
4. KAIN ZN, FERRIS CA, MAYES LC, RIMAR S: Parental presence during induction of anaesthesia: practice differences between the United States and Great Britain. *Paediat Anaesth;* 1996, 6:187-193.
5. SCHULMAN JL, FOLEY JM, VERNON DT, ALLAN D: A study of the effect of the mother's presence during anesthesia induction. *Pediatrics;* 1967, 39:111-114.
6. HANNALLAH RS, ROSALES JK: Experience with parents' presence during anaesthesia induction in children. *Can Anaesth Soc J;* 1983, 30:286-289.
7. RYDER I, SPARGO P: Parents in the anesthetic room: a questionnaire survey of parents' reactions. *Anaesthesia;* 1991, 46:977-979.
8. KAIN ZN, CALDWELL-ANDREWS AA, WANG SM, ET AL: Parental intervention choices for children undergoing repeated surgeries. *Anesth Analg*; 2003, 96:970-975.
9. KAIN ZN, CALDWELL-ANDREWS AA, KRIVUTZA D, ET AL: Trends in the practice of parental presence during induction of anesthesia and the use of preoperative sedative premedication in the United States, 1995-2002: results of a follow-up national survey. *Anesth Analg;* 2004, 98:1252-1259.
10. SHAW EG, ROUTH DK: Effect of mother presence on children's reaction to aversive procedures. *J Pediatr Psychol;* 1982, 7:33-42.
11. BOWIE JR: Parents in the operating room. *Anesthesiology;* 1993, 78:1192-1193.
12. KAIN ZN, MAYES LC, WANG SM, ET AL: Parental presence during induction of anesthesia versus sedative premedication: which intervention is more effective? *Anesthesiology;* 1998, 89:1147-1156.
13. KAIN ZN, MAYES LC, WANG SM, ET AL: Parental presence and a sedative premedicant for children undergoing surgery: a hierarchical study. *Anesthesiology;* 2000, 92:939-946.
14. KAIN ZN, MAYES LC, CARAMICO LA, ET AL: Parental presence during induction of anesthesia: a randomized controlled trial. *Anesthesiology;* 1996, 84:1060-1067.
15. American Academy of Pediatrics: Child life programs. *Pediatrics;* 1993, 91:671-672.
16. KAIN ZN, CALDWELL-ANDREWS AA, MAYES LC, ET AL: Family-centered preparation for surgery improves perioperative outcomes in children: a randomized controlled trial. *Anesthesiology;* 2007, 106:65-74.
17. MELAMED BG, DEARBORN M, HERMECZ DA: Necessary considerations for surgery preparation: age and previous experience. *Psychosom Med;* 1983, 45:517-525.
18. KAIN ZN, MAYES LC, CARAMICO LA: Preoperative preparation in children: a cross-sectional study. *J Clin Anesthesia;* 1996, 8:508-514.
19. RYDER I, SPARGO P: Parents in the anesthetic room: a questionnaire survey of parents' reactions. *Anaesthesia;* 1991, 46:977-979.
20. O'BYRNE K, PETERSON L, SALDANA L: Survey of pediatric hospitals' preparation programs: evidence of the impact of health psychology research. *Health Psychol;* 1997, 16:147-154.
21. RIVA J, LEJBUSIEWICZ G, PAPA M, ET AL: Oral premedication with midazolam in paediatric anesthesia: effects on sedation and gastric contents. *Paediatr Anaesth;* 1997, 7:191-196.
22. KAIN ZN, MAYES LC, BELL C, ET AL: Premedication in the United States: a status report. *Anesth Analg;* 1997, 84:427-432.
23. COTE CJ, COHEN IT, SURESH S ET AL: A comparison of three doses of commercially prepared oral midazolam syrup in children. *Anesth Analg;* 2002, 94:37-43.
24. FELD LH, NEGUS JB, WHITE PF: Oral midazolam preanesthetic medication in pediatric outpatients. *Anesthesiology;* 1990, 73:831-834.
25. RITA L, SELENY FL, MAZUREK A, RABINS SY: Intramuscular midazolam for pediatric preanesthetic sedation: a double-blind controlled study with morphine. *Anesthesiology;* 1985, 63:528-531.
26. SAINT-MAURICE C, LANDAIS A, DELLEUR MM, ET AL: The use of midazolam in diagnostic and short surgical procedures in children. *Acta Anaesthesiol Scand Suppl;* 1990, 92:39-41. discussion 47.
27. SAARNIVAARA L, LINDGREN L, KLEMOLA UM: Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery. *Br J Anaesth;* 1988, 61:390-396.
28. WILTON NC, LEIGH J, ROSEN DR, PANDIT UA: Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology;* 1988, 69:972-975.
29. WALBERGH EJ, WILLS RJ, ECKHERT J: Plasma concentrations of midazolam in children following intranasal administration. *Anesthesiology;* 1991, 74:233-235.
30. GRIFFITH N, HOWELL S, MASON DG: Intranasal midazolam for premedication of children undergoing day-case anaesthesia: comparison of two delivery systems with assessment of intra-observer variability. *Br J Anaesth;* 1998, 81:865-869.

31. MALINOVSKY JM, COZIAN A, LEPAGE JY, ET AL: Ketamine and midazolam neurotoxicity in the rabbit. *Anesthesiology;* 1991, 75:91-97.

32. American Academy of Pediatrics: Alternative routes of drug administration-advantages and disadvantages (subject review). Committee on Drugs. *Pediatrics;* 1997, 100:143-152.

33. MARTLEW RA, MEAKIN G, WADSWORTH R, ET AL: Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam. *Br J Anaesth;* 1996, 76:308-309.

34. VIITANEN H, ANNILA P, VIITANEN M, YLI-HANKALA A: Midazolam premedication delays recovery from propofol-induced sevoflurane anesthesia in children 1-3 yr. *Can J Anaesth;* 1999, 46:766-771.

35. VIITANEN H, ANNILA P, VIITANEN M, TARKKILA P: Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. *Anesth Analg;* 1999, 89:75.

36. BROSIUS KK, BANNISTER CF: Effect of oral midazolam premedication on the awakening concentration of sevoflurane, recovery times and bispectral index in children. *Paediatr Anaesth;* 2001, 11:585-590.

37. KAIN ZN, HOFSTADTER MB, MAYES LC, ET AL: Midazolam: effects on amnesia and anxiety in children. *Anesthesiology;* 2000, 93:676-684.

38. GOLPARVAR M, SAGHAEI M, SAJEDI P, RAZAVI SS: Paradoxical reaction following intravenous midazolam premedication in pediatric patients-a randomized placebo controlled trial of ketamine for rapid tranquilization. *Paediatr Anaesth;* 2004, 14:924-930.

39. RELLING MV, MULHERN RK, DODGE RK, ET AL: Lorazepam pharmacodynamics and pharmacokinetics in children. *J Pediatr;* 1989, 114:641-646.

40. MCCALL JE, FISCHER CG, WARDEN G, ET AL: Lorazepam given the night before surgery reduces preoperative anxiety in children undergoing reconstructive burn surgery. *J Burn Care Rehabil;* 1999, 20:151-154.

41. MANDELLI M, TOGNONI G, GARATTINI S: Clinical pharmacokinetics of diazepam. *Clin Pharmacokinet*; 1978, 3:72-91.

42. ROELOFSE JA, VAN DER BIJL P: Comparison of rectal midazolam and diazepam for premedication in pediatric dental patients. *J Oral Maxillofac Surg;* 1993, 51:525-529.

43. MATTILA MA, RUOPPI MK, AHLSTROM-BENGS E, ET AL: Diazepam in rectal solution as premedication in children, with special reference to serum concentrations. *Br J Anaesth;* 1981, 53:1269-1272.

44. HUDSON RJ, STANSKI DR, BURCH PG: Pharmacokinetics of methohexital and thiopental in surgical patients. *Anesthesiology;* 1983, 59:215-219.

45. YEMEN TA, PULLERITS J, STILLMAN R, HERSHEY M: Rectal methohexital causing apnea in two patients with meningomyeloceles. *Anesthesiology;* 1991, 74:1139-1141.

46. LIU LM, LIU PL, MOSS J: Severe histamine-mediated reaction to rectally administered methohexital. *Anesthesiology;* 1984, 61:95-97.

47. ROCKOFF MA, GOUDSOUZIAN NG: Seizures induced by methohexital. *Anesthesiology;* 1981, 54:333-335.

48. BEEKMAN RP, HOORNTJE TM, BEEK FJ, KUIJTEN RH: Sedation for children undergoing magnetic resonance imaging: efficacy and safety of rectal thiopental. *Eur J Pediatr;* 1996, 155:820-822.

49. REIMCHE LD, SANKARAN K, HINDMARSH KW, ET AL: Chloral hydrate sedation in neonates and infants-clinical and pharmacologic considerations. *Dev Pharmacol Ther;* 1989, 12:57-64.

50. MALVIYA S, VOEPEL-LEWIS T, PROCHASKA G, TAIT AR: Prolonged recovery and delayed side effects of sedation for diagnostic imaging studies in children. *Pediatrics;* 2000, 105:E42.

51. BIBAN P, BARALDI E, PETTENAZZO A, ET AL: Adverse effect of chloral hydrate in two young children with obstructive sleep apnea. *Pediatrics;* 1993, 92:461-463.

52. COTÉ CJ, KARL HW, NOTTERMAN DA, ET AL: Adverse sedation events in pediatrics: analysis of medications used for sedation. *Pediatrics;* 2000, 106:633-644.

53. TAMMINGA RY, NOORDHOEK M, KROON J, FABER-NIJHOLT R: Ketamine anesthesia with or without diazepam premedication for bone marrow punctures in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol;* 2000, 17:383-388.

54. HOLLISTER GR, BURN JM: Side effects of ketamine in pediatric anesthesia. *Anesth Analg;* 1974, 53:264-267.

55. WHITE PF, HAM J, WAY WL, TREVOR AJ: Pharmacology of ketamine isomers in surgical patients. *Anesthesiology;* 1980, 52:231-239.

56. WIEBER J, GUGLER R, HENGSTMANN JH, DENGLER HJ: Pharmacokinetics of ketamine in man. *Anaesthetist;* 1975, 24:260-263.

57. LOCKHART CH, NELSON WL: The relationship of ketamine requirement to age in pediatric patients. *Anesthesiology;* 1974, 40:507-508.

58. HANNALLAH RS, PATEL RI: Low-dose intramuscular ketamine for anesthesia pre-induction in young children undergoing brief outpatient procedures. *Anesthesiology;* 1989, 70:598-600.

59. VERGHESE ST, HANNALLAH RS, PATEL RI, PATEL KM: Ketamine and midazolam is an inappropriate preinduction combination in uncooperative children undergoing brief ambulatory procedures. *Paediatr Anaesth;* 2003, 13:228-232.

60. FUNK W, JAKOB W, RIEDL T, TAEGER K: Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. *Br J Anaesth;* 2000, 84:335-340.

61. WEKSLER N, OVADIA L, MUATI G, STAV A: Nasal ketamine for paediatric premedication. *Can J Anaesth;* 1993, 40:119-121.

62. VAN DER BIJL P, ROELOFSE JA, STANDER IA: Rectal ketamine and midazolam for premedication in pediatric dentistry. *J Oral Maxillofac Surg;* 1991, 49:1050-1054.

63. EGAN TD, SHARMA A, ASHBURN MA, ET AL: Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers. *Anesthesiolog;* 2000, 92:665-673.

64. DSIDA RM, WHEELER M, BIRMINGHAM PK, ET AL: Premedication of pediatric tonsillectomy patients with oral transmucosal fentanyl citrate. *Anesth Analg;* 1998, 86:66-70.

65. EPSTEIN RH, MENDEL HG, WITKOWSKI TA, ET AL: The safety and efficacy of oral transmucosal fentanyl citrate for preoperative sedation in young children. *Anesth Analg;* 1996, 83:1200-1205.

66. BINSTOCK W, RUBIN R, BACHMAN C, ET AL: The effect of premedication with OTFC, with or without ondansetron, on postoperative agitation, and nausea and vomiting in pediatric ambulatory patients. *Paediatr Anaesth;* 2004, 14:759-767.

67. ARMSTRONG PJ, BERSTEN A: Normeperidine toxicity. *Anesth Analg;* 1986, 65:536-538.

68. KHOSRAVI MB, KHEZRI S, AZEMATI S: Tramadol for pain relief in children undergoing herniotomy: a comparison with ilioinguinal and iliohypogastric blocks. *Paediatr Anaesth;* 2006, 16:54-58.

69. PAPPAS AL, FLUDER EM, CREECH S, ET AL: Postoperative analgesia in children undergoing myringotomy and placement equalization tubes in ambulatory surgery. *Anesth Analg;* 2003, 96:1621-1624.

70. NISHINA K, MIKAWA K, SHIGA M, OBARA H: Clonidine in paediatric anaesthesia. *Paediatr Anaesth;* 1999, 9:187-202.

71. RAMESH VJ, BHARDWAJ N, BATRA YK: Comparative study of oral clonidine and diazepam as premedicants in children. *Int J Clin Pharmacol Ther;* 1997, 35:218-221.

72. FAZI L, JANTZEN EC, ROSE JB, ET AL: A comparison of oral clonidine and oral midazolam as preanesthetic medications in the pediatric tonsillectomy patient. *Anesth Analg;* 2001, 92:56-61.

73. SIMONS KJ, WATSON WT, MARTIN TJ, ET AL: Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J Clin Pharmacol;* 1990, 30:665-671.

74. NILSSON A, ENGBERG G, HENNEBERG S, ET AL: Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth;* 1990, 64:72-76.

75. BRISMAN M, LJUNG BM, OTTERBOM I, ET AL: Methaemoglobin formation after the use of EMLA cream in term neonates. *Acta Paediatr;* 1998, 87:1191-1194.

76. SETHNA NF, VERGHESE ST, HANNALLAH RS, ET AL: A randomized controlled trial to evaluate S-Caine patch for reducing pain associated with vascular access in children. *Anesthesiology;* 2005, 102:403-408.

77. ZEMPSKY WT, ASHBURN MA: Iontophoresis: noninvasive drug delivery. *Am J Anesthesiol;* 1998, 25:158-162.

78. GALINKIN JL, ROSE JB, HARRIS K, WATCHA MF: Lidocaine iontophoresis versus eutectic mixture of local anesthetics (EMLA) for IV placement in children. *Anesth Analg;* 2002, 94:1484-1488.

79. ROSE JB, GALINKIN JL, JANTZEN EC, CHIAVACCI RM: A study of lidocaine iontophoresis for pediatric venipuncture. *Anesth Analg;* 2002, 94:867-871.