Procedural Sedation Curriculum Nationwide Children's Hospital Columbus, Ohio

Module 5: Procedural Sedation Overview

INTRODUCTION

Invasive and/or non-invasive procedures remain both a common and necessary component in the management of children with acute and chronic disease. While adults are frequently able to tolerate such procedures without sedation, developmental issues such as stranger anxiety, fear during illness, previous experiences with painful procedures, fear of pain, and the inability to cooperate and/or remain motionless for prolonged periods often mandate the use of sedation for these procedures in children. The actual sedation regimen utilized will depend on both procedure- and patient-related factors.

In recent years there has been a considerable shift in philosophy regarding pediatric procedural sedation. There is an increasing recognition of the negative aspects of inadequate sedation. Surveys of parents and patients with pediatric malignancies have shown that the invasive procedures are often perceived as worse than the disease itself. Therefore, more children are being sedated for procedures, the depth of sedation achieved is increasing in certain environments, and the scope of practitioners performing sedations is widening with an increasing number being performed by non-anesthesiologists. The current chapter will discuss issues regarding procedural sedation in pediatric patients, including factors involved in making a decision to sedate, current guidelines for patient assessment and monitoring during sedation, factors which determine the choice of sedative and/or analgesia, and a discussion of some of the more commonly utilized sedative and analgesic agents within the pediatric population. While the principles discussed apply to both anesthesiologists and non-anesthesiologists, this focus of this chapter will be the non-anesthesiologist practitioner.

DEFINITIONS

In response to the expanding use of procedural sedation by non-anesthesiologists, the American Academy of Pediatrics published in 1985[1], and revised in 1992[2], guidelines for patient monitoring and management in this environment. Included in these guidelines are definitions pertinent to the provision of procedural sedation and analgesia, including the different depths of sedation encountered. These definitions are worth reviewing as they outline some of the important features of sedation as well as enforce the principle that depths of sedation occur along a continuum and that the transition from one into the other, including the associated changes in risks associated with each level, can occur very easily and often without the practitioner's awareness.

Conscious sedation is defined as a "medically controlled state of depressed consciousness or unconsciousness from which a patient is not easily aroused that 1) allows protective reflexes to be maintained; 2) retains the patient's ability to maintain a patent airway independently and consciously; and 3) permits appropriate response of the patient to physical stimulation or verbal command".

Deep (unconscious) Sedation is defined as a "medically controlled state of depressed consciousness or unconsciousness from which a patient is not easily aroused. It may be accompanied by a partial or complete loss of protective reflexes, and includes the inability to maintain a patent airway independently and respond purposefully to physical stimulation or verbal command".

General Anesthesia is defined as a "medically controlled state of unconsciousness accompanied by a loss of protective reflexes, including the inability to

maintain a patent airway independently and respond purposefully to physical or verbal stimulation".

These definitions raise three important points. First, there is significant overlap between each level of sedation and knowledge of when one has passed from one level to the other may be difficult to assess during the procedure, especially if ongoing medications are being administered. However, knowledge of the depth of sedation achieved is important as the risks of adverse events increase with increasing depth of sedation. For this reason, the Joint Commission on Accreditation of Health Care Organization (JCAHO) has dictated that their standards for sedation monitoring be based on depth of sedation, with deeper levels of sedation mandating increased monitoring measures[3]. Second, while we traditionally refer to the use of "conscious sedation" for pediatric procedures, this is somewhat of a misnomer as in many situations, what is really achieved is actually deep or unconscious sedation. Finally, while sedation and analgesia should be considered independently when making decisions regarding a patient's procedure-related needs, the practitioner must be aware that many analgesics used for procedural sedation also have sedative properties and may push the patient from one level of sedation to another.

PRESEDATION ASSESSMENT

Once it has been determined that a patient requires sedation, a presedation assessment is performed. This assessment should achieve 2 goals. First, it must convince the practitioner that the patient is medically fit to be sedated. Assessment of this fitness is divided into two components; the identification of acute illnesses that may

increase the likelihood of complications during sedation and the identification of co-morbidities that either mandate the use of special interventions during the sedation or which place the patient at a sufficiently high of morbidity that sedation is inappropriate and the patient should be referred to an anesthesiologist. Secondly, the assessment should allow the practitioner to determine depth of sedation that will likely be required to effectively complete the procedure and allow the him/her to make an informed decision regarding the agents he/she will use. Ideally then, this assessment should be performed by the individual who will ultimately be providing the sedation. This ensures that the person providing the sedation has first-hand knowledge of the patient and his/her medical needs. It also allows the practitioner performing the sedation to address specific patient concerns prior to the sedation and continue to focus on them while the actual procedure is being performed.

The significant components of the presedation assessment are outlined in Table 1. The determination of the fitness for sedation is accomplished through the performance of a focussed history and physical examination. The history should focus on the child's current state of health as it relates to the reason for why he/she is undergoing the procedure, as well as his/her past medical history in order to identify significant co-morbidities. Since the primary risks associated with sedation include adverse respiratory (e.g. apnea, hypoxemia, and upper airway obstruction) or cardiovascular (e.g. hypotension, dysrhythmias) events, these systems should be particularly focussed on. A complete upper airway assessment should be performed, which includes obtaining a history of sleep obstruction, and an examination of the head and neck designed to identify the patient in whom endotracheal intubation may be more

difficult (eg. short neck or limited neck mobility, micrognathia, macroglossia, trismus).

An objective measure of this includes the Mallampati Scoring System (Figure 1).

Specifically, if the patient is Mallampati Grade III or IV (tonsillar pillars and uvula cannot

be visualized), his/her trachea may be difficult to intubate.   While the possibility of a

difficult airway does not preclude the use of procedural sedation, pediatric

anesthesiology consultation may be considered prior to the sedation and it may be

prudent to ensure that anesthesiology back-up is available when the procedure is

performed. Upon completion of the history and physical examination, an ASA

(American Association of Anesthesiologist) classification may be assigned (Table 2).

Patients with ASA Class III or IV are at higher risk of adverse events when sedated and

pediatric anesthesiology consultation may also be considered in these patients.

It is also important during this assessment to identify the child's previous

experiences with procedural sedation, identifying both their effectiveness as well as the

child's and his/her parent's perceptions of the experiences. Knowledge of previous bad

experiences will help the practitioner in both sedative agent selection as well as help

him/her to address specific patient concerns prior to entry into the procedure room.

Identification of these concerns also enables the practitioner an opportunity to engage

the patient and his/her family in presedation counseling in which the risks, benefits and

limitations of sedation and/or analgesia are discussed. This discussion should include a

description of the agents chosen for use along with specific effects and or behaviors

that the patient and/or parents may anticipate from these agents.

A final and important component of the presedation assessment is an

establishment of when the child last had any oral intake, to decrease the possibility of

aspiration if airway protective reflexes are lost. The American Society of

Anesthesiologists recommends that children be *nil per os* (NPO) for clear liquids for 2-3

hours and for solids for 4-8 hours prior to undergoing sedation for elective procedures

(Table 3)[4]. These guidelines have been increasingly challenged, particularly by those

working in acute-care environments where procedures may need to be performed more

urgently. While published reports from these environments have failed to show an

effect of pre-procedure fasting on the incidence of adverse outcomes, these studies

have been underpowered to truly evaluate this question. Until appropriately powered

studies have adequately addressed this issue, prudence would suggest that one

adhere, as much as possible, to the ASA guidelines. These guidelines should be

reviewed with the parents at the time the procedure is scheduled and should be

reiterated if a reminder phone call is made in the 24-48 hours prior to the actual

procedure date.

PREPARATION FOR SEDATION

Personnel

As mentioned previously, the JCAHO has mandated that the use of deep

(unconscious) sedation requires the same monitoring standards as are used during

general anesthesia. As much of pediatric procedural sedation falls into this category,

special preparation of the sedation environment is required to ensure adherence to

these standards. This includes both the personnel and equipment that must be

available during the sedation. As most of the adverse events that occur during

procedural sedation involve respiratory depression with the potential loss of a patent

airway, one of the most important requirements is that there be at least one person in attendance at all times who is skilled in emergent airway management, including the performance of bag-valve mask ventilation and endotracheal intubation. This person is solely responsibility for observing the patient throughout the procedure, for performing sedation-related assessments and documentation, and should not be at all involved in the procedure itself. In cases where only light sedation is achieved, this person may be a nurse although, when deep unconscious sedation is desired, this person should ideally be a physician.

In response to the Joint Commission's standards, many institutions have implemented sedation credentialing procedures for non-anesthesiologists. While such processes may satisfy regulatory bodies, and may raise the level of awareness of those who go through the process regarding sedative and analgesic medications, they are often more theoretical than practical and may not ensure that the practitioner who completes them can safely attend to all aspects of sedation, including resuscitation. Therefore, individual practitioners must utilize good self-judgment and restrict their use of sedatives to agents with which they are both familiar and comfortable and should also only aim to achieve depths of sedation with which they are proficient at rescuing a patient from. If such proficiency is lacking, practitioners should either consider seeking additional airway experience with their anesthesiology or critical care colleagues or abstain from providing sedation. Finally, while it may not be specifically required, it is recommended that the person monitoring the patient retain up to date certification in Pediatric Advanced Life Support[2].

Equipment

While the incidence of significant complications during procedural sedation should be low, the sedation environment must be prepared in such a way that, should complications arise, they may be addressed immediately. This includes having readily available the necessary equipment and medications to perform such resuscitation. These items should be readily available in the procedure area. If patients are sedated in one area and moved to a second area for their procedure, a stocked equipment cart should either be available in both areas or a portable cart should be available to take with the patient. Both the AAP and the ASA have published suggestions regarding the contents of such a cart, [2,4] which are summarized in Table 4.

Prior to the administration of any sedatives, some equipment should be set out within arms reach including an appropriately sized bag-valve-mask device, Yankauer suction system, and monitoring devices. For when light sedation is desired via oral medications, the placement of an intravenous catheter is optional. However, when deep sedation is planned, even if administered via inhalation or oral medications, a functioning intravenous catheter should be placed.

MONITORING DURING SEDATION:

Monitoring during sedation is most likely to bring to mind the mechanisms put into place to ensure patient safety and stability. While obviously important, such a view is incomplete. Rather, comprehensive monitoring during procedural sedation is more appropriately looked at as assessing two separate but related aspects; patient stability (usually focussed on cardiorespiratory) and patient consciousness/comfort, particularly

during painful or noxious procedures. From a humanitarian standpoint, the importance of comfort is intuitive. However, there is also a growing body of literature supporting the adverse effects of inadequate pain control or comfort measures during invasive procedures, especially in patients requiring multiple procedures such as those with oncologic diagnoses. The increasing number of references to pain as the "5th vital sign" further support the importance of adequately monitoring this variable during the procedure.

Cardiorespiratory Monitoring

As previously mentioned, JCAHO has stated that the administration of sedation, with or without analgesia, which may be reasonably expected to result in the potential for loss of airway protective reflexes, mandates the implementation of anesthesia standards for patient monitoring. This mandate arises out of the recognition that sedated procedures carry with them a risk of adverse events, most commonly cardiorespiratory, and documentation by anesthesiologists that appropriate monitoring may prevent a significant number of negative outcomes[5]. Malviya et al evaluated the incidence of complications in 1140 sedations performed by non-anesthesiologists[6]. Complications other than inadequate sedation occurred in 98 instances (8.6%). Of those complications, 55 were primarily respiratory (4.8%) and 6 were primarily cardiac (0.5%). Fifteen children (1.3%) were reported to have become oversedated. Risk factors for adverse events included age <1 yr and ASA class 3 or 4. Similarly, in an analysis of 95 severe sedation-related adverse events, Cote et al found that respiratory events accounted for over 80% of complications[7].

Based on these experiences, patient vital sign monitoring should focus on both anticipating the potential for respiratory compromise as well as vigilant watchfulness for the development of such compromise. The first and most important component of this is the person actually monitoring the patient. This person should have an unobstructed view of the patient 's face, mouth, and chest wall throughout the procedure and drapes/barriers etc. should not obstruct this view unless completely necessary (i.e. upper central venous catheter insertion, MRI scanning). As most respiratory events occur in the period immediately following the administration of medications, it is particularly important that the monitor physically watch the patient for signs of hypoventilation, decreased chest wall movement, airway obstruction etc during this time as devices such as pulse oximeters may not pick these problems up until the patient has become significantly desaturated.

Formal monitoring should include, at minimum, continuous pulse oximetry and heart rate (via the pulse oximeter or ECG) as well as intermittent recording of respiratory rate and blood pressure[2]. While the frequency of recording is not specified, this should occur at a frequency of at least every 5 minutes during the procedure and may be decreased as the patient regains consciousness during the recovery phase.

However, these monitors all have limitations and the practitioner must be cognizant of them, and not rely on them solely to be assured that his/her patient's status is stable. Pulse oximetry is the most widely used adjunct monitor and has added substantially to our ability to continuously estimate a patient's oxygenation status but have their limitations. Currently available oximeters are calibrated for SaO_2 values over 80% and lose their accuracy at values <75%[8]. While this is clinically unimportant for

most patients, in whom SaO_2 values would normally be in the upper 90% range, this may become significant when sedating patients with residual cyanotic congenital heart disease where SaO_2 values of 70-80% are common.   Also, patient movement may be interpreted as pulsatile flow, resulting in inaccurate readings. Such artifact has been documented in up to 25% of patients monitored with older oximeters[9]. The same movement artifact limitation mandates that care be used when relying upon the oximeter to monitor heart rate. Ideally, pulse oximeters which display the plethysmography tracing should be used. If this is not possible or there are concerns regarding the accuracy of the oximeter, heart rate should be monitored directly with ECG recording. Placement of the oximeter probe on cool extremities has also been associated with decreased accuracy, a factor which may need to be considered during certain invasive procedures in which the patient may be disrobed to varying degrees. Finally, there may be a significant delay between the development of hypoxemia and it's registration by the pulse oximeter. Many of these issues should be decreased by newer pulse oximetry technologies such as Masimo's Signal Extraction Technology[10] and Nellcor's forehead reflectance sensors[11], which appear to be more rapidly responsive and less sensitive to motion artifact and extremity temperature.

Intermittent recording of respiratory rate is best done manually, as this also allows the monitor to determine the effectiveness of the respiratory effort. However, under circumstances when the chest must be obscured by drapes during the procedure (i.e. central venous line insertion), or there is a reasonable risk of respiratory compromise (i.e. flexible fiberoptic bronchoscopy), continuous respiratory monitoring using plethysmography should be implemented. While not required, formal monitoring

of ventilation via end-tidal capnography may also be considered, particularly under conditions where access to the patient is limited, such as during MRI scanning. With this device, reports from the Emergency Department[12] and procedure suite[13] have documented the development of hypercarbia in the absence of clinically apparent respiratory depression or desaturation by pulse oximetry. These data suggest that capnography may facilitate the earlier detection of respiratory compromise and should, perhaps, be utilized more frequently than current practices suggest.

Comfort/Consciousness Monitoring

The need to assure patient comfort during procedures has become increasingly stressed and the concept of pain as the 5th vital sign has gained increasing popularity. Assessment of pain during procedures, however, may be somewhat more difficult, especially in the pre-verbal or non-verbal patient, in whom the etiology (i.e. pain vs irritation vs fear etc) of signs of distress may be difficult. Whereas scoring systems to assess post-procedure, particularly post-operative pain have been well-established, such scoring systems remain limited for the assessment of pain during the procedure. While the lack of movement or struggling during a painful manipulation likely indicates the absence of significant pain, it would be inappropriate to expect that every patient undergoing painful procedures be sufficiently sedated as to lose all responsiveness.

Given previously mentioned concerns regarding the ease with which a patient may slip from light sedation to deep sedation to general anesthesia, accurate assessment and documentation of the depth of sedation achieved throughout the procedure is very important. During light sedation, this may be easily accomplished by manual assessment of the patient's ability to appropriately respond to questions.

However, with deeper sedation, such assessments become of limited utility. To address this issue, a variety of sedation scales have been developed to more quantify the degree of unconsciousness. The Observers Assessment of Alertness/Sedation scale has been validated in children but is limited in it's ability to differentiate between deeper levels of sedation, which is arguably where one would wish such a scale to be the most sensitive[14]. Conversely, other scales such as the Vancouver Sedative Recovery Scale are better at differentiating deeper levels of sedation but are too cumbersome to be easily utilized during short procedures[15]. More recently, Malviya et al developed and validated the University of Michigan Sedation Scale (UMSS)[16]. This scale was developed to be a simple efficient tool to assess depth of sedation over the entire sedation continuum as well as one which could easily be applied by various disciplines of health care providers. It utilizes a simple scale of 0-4 (Table 5) with 0 being an awake, alert patient and 4 indicating unresponsiveness and can easily be performed within seconds.

A major drawback of all these tools is that they require patient stimulation to make an assessment. In patients who have been difficult to sedate or in whom movement during the assessment may interfere with the procedure being performed, this may lead the assessor to inadequately stimulate the patient during the assessment and, therefore, underestimate the true depth of sedation. In light of these concerns, the Bispectral Index (BIS) may be a valuable adjunct to monitoring during procedural sedation. Originally developed for use in the operating room, the BIS monitor processes a modified electroencephalogram (EEG) to assess the hypnotic effects of sedative and anesthetic agents, replacing the reliance on physiological parameters for

determining the depth of anesthesia. A number is assigned between 0 (isoelectric) and 100 (fully awake), making interpretation simple and easily available to any bedside caregiver. The validity of the BIS for determining depth of anesthesia has been well documented in adults[17] and children[18]. More recently, the BIS has also been shown to correlate with depth of sedation during mechanical ventilation in critically ill children[19,20]. To date, there are few data evaluating the BIS during procedural sedation. Gill et al compared BIS values with Ramsay sedation scores in 37 adult Emergency Room patients receiving procedural sedation and/or analgesia[21]. The authors reported a significant correlation between BIS and depth of sedation but noted a wide variability in BIS values at similar sedation scores. They did report that the BIS was most effective at differentiating moderate-to-deep sedation from general anesthesia, which is arguably one of the more important distinctions being sought. Brown McDermott et al compared BIS values with UMSS scores in 86 children ≤ 12 yrs of age[22]. The authors reported a good correlation between BIS value and sedation score, including in patients less than 6 months of age. However, they reported that the correlation was somewhat agent-dependent with patients receiving either ketamine or a combination of oral chloral hydrate/hydroxyzine/meperidine showing poorer correlation. While further study is required, these studies suggest that the BIS may add useful information in this environment, especially during lengthy procedures (i.e. MRI, nuclear medicine) or when drug infusions (vs intermittent dosing) are employed, and the risk of inadvertent oversedation may be increased.

Post Procedure Monitoring and Discharge Criteria

While the greatest risk of adverse events occurs at the time of sedative administration, continued cardiorespiratory and neurologic monitoring in the post-procedure period remain very important. It is often during this period that sedation-related nausea may occur and, if this is sufficient to cause vomiting prior to the patient regaining consciousness, the risks of pulmonary aspiration may be increased. In addition, it is possible that sedative-induced respiratory depression is suppressed during the procedure while the patient is being manipulated only to manifest post-procedure when the patient is left alone.

In the initial post-procedure period, monitoring should continue to include continuous pulse oximetry and heart rate monitoring and intermittent recordings of blood pressure and respiratory rate. Depth of sedation should also continue to be assessed frequently. As consciousness is regained, the frequency with which these assessments are done may be decreased although it is recommended that pulse oximetry remain in place until the patient is at or near baseline. Discharge criteria have been established by both the AAP and the ASA[2,4]. These criteria require that the patient be back to their baseline from a neurologic standpoint, that their vital signs are normal (Table 6). It is also prudent to assure that the patient has been able to tolerate oral intake for a certain time period in order to limit the likelihood of dehydration from protracted vomiting. A phone number, preferably to contact someone familiar with sedation practices and the management of post-sedation complications should also be provided.

CHOICE OF AGENT(S)

Once a decision has been made to provide sedation and/or analgesia for a procedure, an agent(s) must be chosen. The ideal sedative agent would have the following characteristics: rapid onset of action, predictable duration, no active metabolites, rapid cessation of effects once discontinued, multiple delivery options, easily titratable, large therapeutic index, minimal cardiopulmonary interactions, minimal drug interactions, and be minimally affected by renal or hepatic disease. Unfortunately, such an agent does not exist. The decision as to which agents are utilized will be based on a number of factors. These factors include, but are not limited to 1) the procedure being performed (type and duration), 2) the depth of sedation required, 3) the need for IV access, 4) the patient's previous experiences with sedation or anesthesia, and 5) risk factors identified in the predation assessment.

Procedures can be broken up into two groups – invasive, for which both sedation and analgesia are often required (eg lumbar puncture, fracture reduction, endoscopic evaluations), and non-invasive, for which sedation alone is often sufficient (eg. radiologic evaluations such as CT or MRI scanning). A list of the more commonly sedated procedures in each of these groups is found in Table 7. Within each of these groups, the practitioner must realize that there is no magic medication that works well in all patients. For example, the medication choice for an MRI evaluation or lumbar puncture may be very different in an otherwise healthy 10 year old compared to a behavior-disordered, developmentally delayed 4 year old. In addition, there may be considerable variation between patients in the dose of a particular drug required to achieve a specific depth of sedation. Therefore, while each agent has it's suggested

dose range, these ranges are better looked at as guidelines with the drug being titrated to the desired effect based on these guidelines.

The route of delivery of the sedative drug is also extremely important, particularly in children who do not require IV access for the procedure itself. In these situations, nonparental administration may be appropriate as many children view having an IV started or an intramuscular (IM) injection given to be as invasive as the procedure itself. For example, chloral hydrate is a popular choice for radiologic procedures. Many physicians are familiar and comfortable with it, it has a good safety profile, and doses of 75 to 80 mg/kg (orally or per rectum) are effective in up to 90% of patients. However, onset times vary from 15 to 60 minutes and, while most children are awake and responsive within 60 to 90 minutes, sedation may be prolonged and last up to 6 hours. This degree of variability must be taken into consideration when using such drugs, especially for short procedures (eg CT scan). In these situations, it may be reasonable for the patient and/or his/her family to conclude that the inconvenience of an IV start is an acceptable price to pay for the ability to utilize a short-acting IV medication. With the availability of topical anesthetic agents to facilitate IV starts (see below), this option becomes even more attractive and should at least be presented to the family when discussing the overall sedation plan.

While this chapter will not provide a recipe of specific sedative agents for specific procedures, it is worthwhile to specifically mention issues related to sedation for cardiac catheterization as many sedative and analgesic agents may alter cardiovascular parameters, such as heart rate, blood pressure, or vascular resistance. It is imperative to consider the underlying cardia lesion and determine how such changes might affect

the both the child's hemodynamics and safety as well as their effect on the data obtained during the procedure. The majority of diagnostic, non-interventional catheterizations are performed with conscious or deep sedation. In infants and young children, this may include an initial dose of chloral hydrate (75 to 100 mg/kg) supplemented with intermittent doses of a benzodiazepine (midazolam 0.05 mg/kg) or an opioid (morphine 0.05 mg/kg) and a mixture of local anesthetics cream to the groin to minimize discomfort during vessel cannulation. Alternative agents for patients who cannot be adequately sedated with the above agents include ketamine, propofol, or the intramuscular mixture of chlorpromazine, meperidine, and promethazine. Because of its negative inotropic properties, propofol should be used only in patients with stable cardiovascular function. Due to limited patient accessibility during cardiac catheterization, it may also be wise to secure the airway if this agent is used, making general anesthesia a more appropriate choice.

SPECIFIC AGENTS

The list of agents available to both the anesthesiologist and the non-anesthesiologist has significantly increased over the past number of years and newer agents are continuing to be developed which may also have a role here. While recognizing that there will be some overlap, these agents may be generally grouped into 3 categories; sedatives, analgesics, and anesthetic agents. A summary of these agents, routes of administrations, doses, and indications is provided in Table 8. The remainder of this chapter will be devoted to a discussion of these specific agents.

SEDATIVE AGENTS

As mentioned previously, these agents are generally required for non-invasive procedures where patient anxieties or developmental abilities make cooperation for procedures that require minimal or no motion difficult. As pure sedatives have no analgesic properties, they should not be used alone for painful procedures, although they are often combined with an analgesic agent for such procedures.

Chloral Hydrate

Chloral hydrate is an alcohol-based sedative-hypnotic agent with no analgesic properties. Because of the extensive experience with this drug, it's ease of administration, and safety profile, it remains one of most popular sedative agents currently used in the pediatric population, especially in infants. Recommended doses range from 30 to 100 mg/kg (maximum 2 g) although the likelihood of sedation failure increases with doses under 60 mg/kg[23]. Chloral hydrate may be administered either orally or rectally. While efficacy and onset of action appear to be more predictable with oral administration, rectal administration may be required in some children due to the drugs unpalatable taste. It is most commonly used for sedation during radiologic or echocardiographic evaluations.

Chloral hydrate is rapidly absorbed from the GI tract and metabolized to the active compound, trichloroethanol, which is hepatically metabolized to the inactive trichloroacetic acid. The mean time to onset of sleep is 25 minutes although a wide range (5-120+ minutes) has been reported[23,24]. Similarly, the mean duration of sleep is 60-90 minutes but may last as long as 6-8 hours. While it has been generally felt that chloral hydrate produces a relatively lighter depth of sedation compared to other agents,

Malviya et al reported during a more formal evaluation of depth of sleep that a significant number of patients sedated with chloral hydrate (50-75 mg/kg) fell into the deeply sedated range[16].

One of the most often discussed advantages of chloral hydrate is it's favorable cardiorespiratory profile, with most reports confirming minimal if any adverse respiratory or hemodynamic events. However, significant hypoxemia from obstruction during sleep and death from respiratory depression have been reported[25]. Due to it's long half life, children should also be monitored following the procedure until fully awake as mortality has been reported in patients discharged home before being fully awake after receiving chloral hydrate[26]. Ventricular dysrhythmias have also been reported, particularly when administered with other prodysrhythmic drugs (i.e. phenothiazines or tricyclic antidepressants), and are believed to be related to the trichloroethanol, which is a halogenated hydrocarbon. More common adverse events include GI upset/vomiting (6-7%), ataxia (17%), and paradoxical agitation (2-18%)[23,24]. The latter reaction can be particularly upsetting for both the parents and care providers. This reaction has been associated with both increasing age (especially >5-6 yr), and underlying neurologic diagnoses and it may be prudent to seek other alternatives in these patient populations.

Benzodiazepines

Benzodiazepines are anxiolytic, sedative-hypnotic agents. They produce antegrade and retrograde amnesia, muscle relaxation, and sedation but have no analgesic properties. They induce sedation via potentiation of chloride currents via neuroinhibitory $GABA_A$ receptors. They are commonly used as sole agents for both

anxiolysis and/or sedation or in combination with other agents (i.e opioids, ketamine) for painful procedures.

There are three commonly used benzodiazepines- lorazepam, diazepam, and midazolam. While all three drugs are effective, lorazepam and diazepam both have a relatively lengthier duration of action, and diazepam causes pain on injection due to the propylene glycol in which it is dissolved. Conversely, midazolam is water soluble, so there is no pain with IV administration, has multiple effective delivery routes, and a shorter elimination half-life than diazepam and lorazepam. Therefore, it has become the benzodiazepine of choice for procedure-related applications. Due to it's rapid onset of action and short duration, midazolam should be administered IV if access is already present. Sedation and anxiolysis are produced within minutes of administration of 0.05 to 0.1 mg/kg and the duration of action is 30-60 min. For minor procedures with which IV access is not required (or desired) non-parenteral routes may be utilized. Oral administration of 0.5 to 0.7 mg/kg produces anxiolysis in 15-20 minutes and is currently the preferred agent for premedication in the operating room. The mean duration of action is 60 minutes (range 45-120 min)[27]. The primary disadvantage to oral administration is that the IV preparation (5 mg/ml) must be used which contains the preservative, benzyl alcohol, which gives the drug a very bitter taste. This taste may be masked by mixing the drug in extra-strength Kool-Aid, acetaminophen elixir, or other sweet/syrupy solutions. Alternative non-parenteral administration routes include intranasal and sublingual. The dose is lower compared to the oral route (0.2-0.4 mg/kg). Midazolam is rapidly absorbed across both mucosal surfaces with sedation occurring in as little as 5 to 10 minutes. With intranasal administration, the patient may

object as the benzoyl alcohol may burn the nasal mucosa. This is avoided with sublingual administration but issues of taste and patient cooperation may limit the usefulness of this route.

Midazolam has wide margin of safety. When used as a sole agent, cardiorespiratory suppression is rare and sedation tends to be lighter, with many patients remaining awake but calm and cooperative after administration of recommended doses.   While this may limit the utility of midazolam in younger children for procedures in which minimal movement can be tolerated, these properties make it an ideal agent for the older child who simply requires anxiolysis. When administered with other agents, particularly opioids, significant respiratory depression can occur[28-30]. Similarly, hypotension is uncommon with midazolam alone but can occur when combined with opioids. Paradoxical excitement or delirium can occur with lower doses, particularly if pain is present.

α-Receptor Antagonists

While α-receptor antagonists have been in clinical use for some time, they have not to date played a role in procedural sedation. However, a recently developed specific α_2 receptor antagonist, dexmedetomidine, has the potential for useful applications in this field. Dexmedetomidine is primarily a sedative agent although it has been shown decreases opioid use in the peri-operative period, suggesting analgesic properties as well[31]. It provides effective sedation during mechanical ventilation in adults[31] and children[32] although experience in the latter group is limited. *(Aside – once the dex-midaz report is accepted, we can use it as the reference here instead - #32)*

Being specific for the α_2 receptor, dexmedetomidine offers the advantages of sedation with fewer cardiovascular effects compared to it's relative clonidine. It also offers the advantage of minimal respiratory suppression[33] and a relatively short elimination half-life (2 hours). Given these properties, we have recently begun to use this agent for sedation during MRI examinations. Sleep is effectively induced with a loading dose of 0.5-1.0 *u*g/kg, and maintained with an infusion of 0.5-0.75 *u*g/kg/hr. The loading dose is administered over 10 minutes as more rapid infusions may cause significant bradycardia or hypotension[34]. The development of bradycardia appears to be exaggerated in patients concurrently taking digoxin[35], although the presence of this effect with other chronotropically active agents remains unknown. Sleep develops without the agitation that often accompanies sedation with chloral hydrate or sodium pentobarbital and recovery is smooth as well. While further data are required, dexmedetomidine appears to offer a safe, effective, and appealing option for sedation during non-invasive procedures.

ANALGESIC AGENTS

Opioids

Several opioids have been used for sedation and analgesia during pediatric procedures and they remain one of the most commonly prescribed classes of analgesics in this setting. Opioids provide analgesia, varying degrees of sedation (i.e. morphine) but no amnesia. Therefore they are frequently combined with a benzodiazepine for procedural sedation. As has been discussed previously, this combination may be associated with significant respiratory depression so appropriate

monitoring must be utilized and resuscitative equipment readily available during these sedations.

The most commonly used opioids in this setting are morphine, meperidine, and fentanyl. Due to their relatively long duration of action (2-4 hours) morphine and meperidine have significant limitations in this setting[36]. This may leave the patient at risk for adverse respiratory events for a significant period of time after the procedure is completed when there is little stimulus to keep the patient awake and when vigilance and monitoring may be more relaxed. Fentanyl is a synthetic opioid with a potency 100 times that of morphine. It is a pure analgesic with no sedative properties. It is highly lipid soluble, which allows rapid penetration across the blood/brain barrier and a rapid onset of action. It is rapidly metabolized with a duration of action of 20-30 min, making it an attractive option for short procedures such as lumbar punctures or fracture reductions.

The most significant adverse effects of opioids are respiratory depression and hypotension. The risks of respiratory depression are similar with equipotent doses of morphine and fentanyl. A concern, however, with fentanyl is that it comes only as a 50 *u*g/ml preparation so small volumes are used in small children, increasing the risk of an inadvertent overdose. Fentanyl is administered in increments of 0.5-1.0 *u*g/kg every 2-3 minutes and titrated to effect. Rapid administration, especially of higher doses, may also in chest wall muscle rigidity.

Fentanyl is also available in a transmucosal preparation. The drug is incorporated into a raspberry flavored lozenge that resembles a lollipop, called the Fentanyl Oralet. Three sizes are available: 200, 300, 400 *u*g. Sedation results

specifically from transmucosal absorption as gastric bioavailability is limited (5-10%).

Therefore, if the child chews or swallows the lozenge it is unlikely to result in any

adverse effects. Onset of analgesia and sedation generally occurs in 10 to 15 minutes.

It has been most frequently used as a preoperative medication in doses of 10 to 20

*u*g/kg although more recent applications have included oncologic procedures[37] and

laceration repair[38]. Dosages in these settings range from 8-20 *u*g/kg and in one study

the oralet was combined with oral midazolam[38]. Effective sedation was reported in each

study although at the higher doses, adverse effects were common, including pruritis

(65%), nausea and vomiting (31%), or desaturation (7%)[37]. While the oralet is no longer

commercially available, a newer preparation, Actiq, is now available, which also

provides fentanyl in a similar formulation. It is available in dosages of 200,400, 600,

800, 1200, and 1600 *u*g. It is currently only approved for use in treating cancer-related

pain and no data yet exist regarding it's use in a procedure-related setting.

Remifentanil is an ultra-short acting synthetic opioid, which has become more

recently available. It has a half-life of 8-10 minutes, which has made it popular for

intraoperative applications. Subsequently, interest has developed in using this agent for

procedural sedation. Remifentanil is administered as an infusion in a dose range of

0.05 to 0.1 *u*g/kg/min, with or without an induction bolus of 0.2 to 1 *u*g/kg over 2 to 5

minutes. As remifentanil has no amnestic properties, an amnestic agent is often added.

To date, remifentanil has been combined with midazolam[30] or propofol[39,40] to provide

sedation for lumbar punctures, fracture reductions, and flexible fiberoptic bronchoscopy.

These regimens have provided good sedation and with rapid recovery times (5-20

minutes). However the reported incidence of respiratory depression or desaturation

with these regimens was relatively high (20-25%), which may limit widespread use of this drug. Other reported adverse effects include nausea/vomiting and pruritis, both of which are uncommon.

Ketamine

Ketamine is dissociative anesthetic chemically related to phencyclidine.[41] Unlike the previously mentioned agents, it provides a combination of sedation, analgesia and amnesia. It is metabolized in the liver and has an active metabolite (norketamine), which has 1/3 the analgesic potency of the parent drug. Interestingly, analgesia with orally administered ketamine occurs at a lower plasma level than with intramuscular administration, likely as a result of higher concentrations of norketamine being produced from first-pass hepatic metabolism with oral administration.

The advantages of ketamine include a relatively short duration of action (15-30 minutes), multiple routes of administration and favorable cardiorespiratory profile. Ketamine produces minimal respiratory depression and has bronchodilating properties, making it an attractive agent for airway invasive procedures or in patients with reactive airways disease. As it stimulates the release of endogenous catecholamines, ketamine causes an early and transient elevation of heart rate and blood pressure. Cardiovascular depression is uncommon and should occur only in patients with catecholamine-depleted states. Due to the excellent analgesia produced, ketamine has become a popular agent for painful or invasive procedures including fracture reductions, invasive line insertions, oncologic procedures, and endoscopies[42-44]. Experience with ketamine administration via the oral[45] or IM[46] routes has also been positive.

Despite providing excellent sedation and analgesia, ketamine has a wide profile of unpleasant side effects. It increases the production of upper airway secretions and should therefore be accompanied by an anti-sialogogue (glycopyrrolate or atropine). It can impair the gag reflex, warranting cautious use in patients with gastroesophageal reflux or full stomachs. Nausea and vomiting are not infrequent and premedication with an antiemetic may be considered, particularly in patients with a history of vomiting. While respiratory depression is uncommon, apnea and laryngospasm have also been reported. Apnea appears to be most common in younger children, which has prompted some to exclude children less than 3 months of age from ketamine protocols[46]. However, we recently reported the safe and efficacious use of ketamine for infant flexible bronchoscopy, suggesting that ketamine may be safely administered to this population[47]. The most frequently discussed adverse effects of ketamine are emergence delirium and/or frank hallucinations. These occur more commonly if ketamine is used alone and in older patients. While many patients will still experience dysphoria during recovery, the concurrent administration of a benzodiazepine with ketamine is very effective in eliminating the occurrence of true delirium or hallucinations. While early reports showed that ketamine can increase intracranial pressure, more recent reports suggest that this ICP response is blunted or obliterated when a benzodiazepine is added[48], allowing ketamine to remain an option for sedation during lumbar pressure when an opening pressure is desired. While the effects of ketamine on patients with seizures remain unclear, numerous reports of seizure occurrences during ketamine sedation have lead many clinicians to view a seizure disorder as a relative contraindication to ketamine.

While ketamine alone is sufficient to induce deep sedation, amnesia, and excellent analgesia, due to the associated hypersalivation and emergence reactions, it should usually be used in combination with an anti-sialogogue (i.e. glycopyrrolate) and a benzodiazepine (i.e. midazolam). Intravenous use is preferred if IV access is available as the onset of action is rapid (1-2 minutes) and the recovery time is short (30-60 minutes). Midazolam (0.05 to 0.1 mg/kg), and glycopyrrolate (5 to 10 µg/kg) are administered 3 to 5 minutes before ketamine. The initial dose of ketamine is 0.5 to 1 mg/kg. Additional doses of 0.5 mg/kg may be administered every 3 minutes to both achieve and maintain desired levels of sedation and analgesia. The initial dose for IM administration is 4-6 mg/kg. The 100 mg/ml preparation of ketamine should be used for this to decrease the injected volume and atropine, 10 ug/kg, may be mixed with the ketamine prior to injection. Additional injections of 2-4 mg/kg of ketamine may be administered after 5-10 minutes if adequate sedation is not achieved. For oral administration, 10 mg/kg is used. The drug may be mixed in a small amount of a clear fluid to make it more palatable. Moderate to deep sedation occurs in 30-45 minutes. Emergence reactions have not been a significant problem with either IM or oral ketamine, even without concomitant administration of midazolam.

ANESTHETIC AGENTS

Barbiturates

Barbiturates remain commonly used agents for the intravenous induction of anesthesia. They are potent respiratory depressants so appropriate airway management skills and monitoring for deep sedation are required when using these

drugs. The three most commonly used agents are methohexital, thiopental, and pentobarbital. Like benzodiazepines, barbiturates provide sedation and amnesia without analgesia. Consequently, they are useful only for nonpainful procedures, especially radiologic procedures, such as CT or MRI.

Methohexital is a short-acting oxybarbiturate with a long history of use as a PR induction agent in children. It has also been used extensively as a sedative for CT or MRI imaging[49]. The standard rectal dose is 20-30 mg/kg. Onset of sleep is rapid (6-10 minutes) with recovery to baseline occurring by 1.5 to 2 hours post administration. Sedation was adequate to perform the evaluation in 80-85% of patients. Significant complications are uncommon with mild respiratory depression responsive to repositioning and/or supplemental oxygen occurring in up to 4% of patients. The duration of action with intravenous use (0.75-1.0 mg/kg) is roughly 10 minutes, making the drug attractive for short procedures such as CT scans. However, the incidence of respiratory depression is greater with this route of administration, which may limit it's usefulness. Methohexital has been reported to precipitate seizures in patients with underlying seizure disorders.

Thiopental is another short-acting barbiturate and is the most commonly used barbiturate for the intravenous induction of anesthesia. Like all barbiturates, thiopental has negative inotropic and vasodilatory properties that can result in hypotension, especially in the setting of hypovolemia or underlying cardiovascular dysfunction. Rapid redistribution accounts for its short duration of action (5 to 10 minutes) after intravenous administration. It is a potent anticonvulsant and may be safely administered to patients with seizure disorders. It has also been used as a rectal agent for sedation for

radiologic procedures in doses of 25-50 mg/kg[50,51]. The depth of sedation achieved is somewhat deeper than with methohexital, and reported success rates for procedures are somewhat higher (>90%). The onset of action is slightly longer (15-30 minutes) with a similar duration of action (60-90 minutes) compared to methohexital.

Sodium pentobarbital is a longer acting barbiturate than either methohexital or thiopental and remains a popular choice for intravenous sedation during radiologic procedures, especially MRI. Multiple delivery options are available including IV, IM, and enteral although IV remains the most commonly used. For IV administration, pentobarbital should be given in increments of 1-2 mg/kg every 3-5minutes until sleep is induced (average total dose 4-5 mg/kg)[52]. The average duration of sleep after induction is 60-90 minutes, which is adequate to perform routine MRI evaluations. Respiratory depression and hypotension may occur, especially with rapid inductions, but are generally mild. A drawback to pentobarbital sedation is that recovery to discharge criteria may be long (2-4 hours) and may be associated with significant agitation, which can be disturbing to both parents and caregivers.

Propofol

Propofol is an anesthetic agent with sedative and hypnotic but no analgesic properties. It produces dose-dependent levels of sedation varying from conscious sedation to general anesthesia. It's mechanism of action is unknown. It is only available for intravenous administration. It has a rapid onset and a short duration of action (5-10 minutes) so recovery is rapid. Because of this, an infusion is generally needed for all but the briefest procedures. Propofol also offers the advantage of being relatively non-emetogenic. Propofol decreases cerebral metabolic rate for oxygen and

intracranial pressure, making it an attractive agent for use in patients with intracranial hypertension.

Adverse effects associated with propofol are similar to those associated with other sedatives. Propofol can cause cardiovascular depression and hypotension, related to both negative inotropic and vasodilatory properties[53]. Respiratory depression is dose-dependent and apnea can be easily induced with excessive or rapid bolus dosing. Other reported CNS effects include opisthotonus, myoclonus, and seizures although propofol also has anticonvulsant properties[54]. Propofol also has a high incidence of causing pain on injection, particularly when injected into the small veins on the dorsum of the hand[55]. Options to decrease this include the administration of a small dose of fentanyl (0.5 to 1 µg/kg) or lidocaine (0.2 to 0.5 mg/kg) before injection or cooling the solution before injection. Due primarily to it's cardiorespiratory effects, propofol remains restricted to anesthesia personnel in some institutions.

For all but the shortest procedures, propofol is generally administered as a bolus induction followed by an infusion. For radiologic or non-painful procedures propofol may be used as a single agent. For short painful procedures, such as lumbar punctures, the addition of an analgesic agent such as fentanyl (1 *u*g/kg) should be considered. As individual responses vary from patient to patient, sedation should be induced using intermittent boluses of 0.5 to 1 mg/kg every 1-2 minutes until adequate sedation is achieved (usually 1-3 mg/kg total). For brief procedures, continued use of intermittent bolus doses (0.5 to 1 mg/kg) may be used whereas for longer procedures, sedation may be maintained with an infusion of 60 to 300 µg/kg/min[56].

Nitrous Oxide

Nitrous oxide has many of the characteristics of a desirable sedation agent. It has a rapid onset of action, is relatively easy and inexpensive to use, and its effects dissipate rapidly once discontinued. Its solubility characteristics allow rapid induction and awakening. It has sedative/hypnotic, amnestic, and analgesic properties. It has been in clinical use as an anesthetic agent for over 150 years but also has extensive an extensive history of use procedural sedation, primarily in the Emergency Department or Dental Suite.

Nitrous oxide can be administered using either a demand-flow (face mask only) or free-flow (face mask or nasal cannula) gas system in concentrations of 30-70%. With the demand flow system, gas flow only occurs when the patient is sufficiently alert to hold the mask to his/her face and create a negative inspiratory pressure. This system effectively prevents inadvertent oversedation but does preclude it's use in the younger (< 5 or 6 years) or developmentally challenged child. To prevent the delivery of a hypoxic gas mixture, an in-line FiO_2 monitor should be in place as well as a mechanism to cut off nitrous oxide flow if the oxygen supply fails. Alternatively, commercially available tanks are manufactured that contain a 50/50 mixture of oxygen and nitrous oxide. A scavenger device attached to the delivery system is required to remove waste gases and prevent environmental pollution.

When administered at standard concentrations, nitrous oxide can cause mild hypotension. There is no effect on the ventilatory response to carbon dioxide, so respiratory depression should not occur. However, nitrous oxide is much more soluble in blood than nitrogen and therefore continues to diffuse into the alveoli after gas

administration has been discontinued, leading to the potential for diffusion hypoxemia. Therefore, 100% oxygen is routinely administered when nitrous oxide is discontinued. Nitrous oxide diffuses quickly into air filled spaces, increasing the volume of the space, and is therefore contraindicated in bowel obstruction and intrathoracic injuries with the risk of pneumothorax. Nitrous oxide causes a mild increase in cerebral blood flow and ICP and is relatively contraindicated in patients with closed head injury and altered intracranial compliance. Repeated exposure of the patient or healthcare workers to nitrous oxide can lead to bone marrow suppression and peripheral neuropathy as a result of its effects on B_{12} metabolism and protein synthesis.

Nitrous oxide has been safely and extensively used for pediatric dental sedation. In 1962, Holst reported no serious complications in 3 million pediatric dental patients treated with 30 to 60% nitrous oxide[57]. Subsequent reports continue to confirm it's safety in this setting. Griffen et al described safe and successful use for Emergency Room management of burns, lacerations, and fracture reductions[58]. More recently, Luhmann and colleagues compared continuous-flow nitrous oxide with or without oral midazolam in 204 children requiring laceration repair[59]. They reported both regimens to be safe and efficacious although the addition of midazolam offered no benefits and was associated with longer discharge times and sustained adverse effects including ataxia, dizziness, and irritability.

COMBINATIONS OF AGENTS

Lytic Cocktail

DPT or the "Lytic Cocktail" is a combination of meperidine (Demerol), promethazine (Phenergan), and chlorpromazine (Thorazine) in a roughly 2:1:1 mixture. The mixture produces both sedation and analgesia. The specific combination developed from findings that opioid analgesia was potentiated by chlorpromazine, thus facilitating analgesia at lower opioid doses. The mixture was initially used for sedation for cardiac catheterization procedures over 40 years ago[60] and it remains a popular choice for these procedures.

Unfortunately, the synergism between constituents that accounts for the mixture's analgesia and sedative effects, also produces many undesirable side effects. All three agents are relatively long acting and sedation may be prolonged. Terndrup et al reported an average time to ED discharge of 4.7 hrs and to return to normal behavior of 19 hours in 63 ED patients[61]. In addition, 29% of their patients were inadequately sedated! The mixture may cause significant respiratory depression, which may occur long after the procedure is completed. Phenothiazines are vasodilators and may cause hypotension. Seizures have been reported and are related to the active metabolite of meperidine, normeperidine, which has been shown to accumulate with the concomitant use of chlorpromazine[62]. Other adverse CNS effects include dystonic reactions, which are also related to the phenothiazines.

Due to these adverse effects and the development of safer and more effective sedative regimens, there is growing belief that this mixture has become outdated. In 1995, the Committee on Drugs of the American Academy of Pediatrics issued a policy

statement on the Lytic Cocktail which, while not quite suggesting it be banned, recommended that alternative sedative and analgesic regimens should be considered[63].

OPIOID AND BENZODIAZEPINE REVERSAL AGENTS

While careful monitoring of drug administration and vigilant patient monitoring should decrease the likelihood of adverse events, these events still can and do occur. Intrapatient responses to sedative agents are not universal and human error can never be completely eliminated. For these reasons, the availability of specific antagonists for opioids and benzodiazepines has enhanced the safety of procedural sedation.

Opioid Antagonists

Two opioid receptor antagonists are available. Naloxone is the most familiar of these two. It is a competitive antagonist of both the mu, kappa opioid receptors, resulting in reversal of analgesia, respiratory depression and sedation[64]. It may be administered via the IV, IM, or endotracheal routes although IV is preferred. The mean duration of action with IV administration is 45 to 60 minutes but ranges from 15 minutes to hours and is dose-dependent. This is shorter than the duration of action of many opioids so continued monitoring must remain in place until the effects of the original drug are dissipated in order to avoid the recurrence of sedation and respiratory depression. Naloxone can precipitate full-blown withdrawal reactions including seizures when given to patients who are opioid dependent and may completely reverse the analgesia produced by the original opioid given. Therefore, naloxone should be administered in small doses and titrated to clinical effect. The starting dose is 1 to 2 μg/kg (maximum 0.2 mg) and may be repeated every 2 to 3 minutes until the desired

effect is achieved.   Slow injection and careful titration of the dose can maximize

reversal of respiratory depression while minimizing analgesia reversal.

Nalmafene is a more recently developed opioid antagonist. It has the same

receptor binding profile of naloxone but it's duration of action is 2-3 hours[65].

Intravenous dosing is 0.25ug/kg every 2 minutes up to 4 doses as clinical benefit

beyond a cumulative dose of 1 ug/kg has net been reported. Experience in pediatric

patients is limited but suggests that it is both effective and safe[66].

Benzodiazepine Antagonists

Flumazenil is the only benzodiazepine antagonist currently available for clinical

use. It competitively binds to central benzodiazepine receptors, thereby inhibiting

gamma amino butyric acid (GABA) receptor activation[67]. Whereas naloxone and

nalmafene reverse both sedation and respiratory depression, flumazenil primarily

reverses sedation with less effect on respiratory depression.   Flumazenil is only

recommended for IV administration and for acute benzodiazepine intoxications. It is

relatively lipophilic so it's onset of action is rapid, within 1-2 minutes. Similar to

naloxone, it's duration of activity (40-80 minutes) is shorter than that of most

benzodiazepines so there is a risk of resedation[68].   The standard dose is 0.01 to 0.02

mg/kg every 1-2 minutes to a maximum of 1.0 mg. Adverse effects occur in

approximately 5% of patients. Common effects include agitation, crying, aggression,

headache, nausea and dizziness. Flumazenil is contraindicated in patients receiving

chronic benzodiazepine therapy, as it may precipitate seizures or withdrawal. Seizures

may also occur if flumazenil is given to patients who have ingested medications which

lower the seizure threshold (eg tricyclic antidepressents, methylxanthines,

cyclosporine). Flumazenil has been reported to precipitate ventricular dysrhythmias when administered concomitantly with cocaine, methylxanthines, monoamine oxidase inhibitors, chloral hydrate, tricyclic antidepressants. Reported pediatric experience is limited, particularly with respect to procedural sedation. Shannon et al administered flumazenil to 107 pediatric patients following sedation with midazolam ± an opiate (85%)[68]. Ninety-six percent of the patients responded to flumazenil at a mean dose of 0.017 mg/kg. Seven patients experienced resedation 19-50 minutes following flumazenil administration. There were no significant adverse events.

Despite the efficacy of both naloxone and flumazenil in reversing the sedative and respiratory depressant effects of opioids and benzodiazepines, their availability does not diminish the need for prompt detection of hypoventilation and the ability to intervene by establishing an airway and assisting ventilation.

TOPICAL AND LOCAL ANESTHETICS

While systemic sedative agents play a vital role in relieving procedure-related anxiety and discomfort, appropriate topical preparation of the invasive procedure site is very important and can significantly decrease or even eliminate the need for parenteral sedation. This may include the application of a topical anesthetic agent to the skin with or without subsequent infiltration with a local anesthetic agent.

EMLA cream (Eutectic Mixture of Local Anesthetics) is the most commonly used topical anesthetic. It is a mixture of two local anesthetics, lidocaine and prilocaine, formulated into a cream. It is applied to the skin using 1-2 grams per 10 cm^2 and covered with an occlusive dressing. A thick deposit is more effective than a thin layer[69].

The depth of penetration is dependent on the duration of contact with the skin – a 4-5 mm depth of penetration is achieved 45-60 minutes after application to intact skin[70]. Analgesia is maintained for up to 30-60 minutes following removal of the cream. This analgesia may be sufficient for superficial procedures and may facilitate painless deep infiltration of a local anesthetic for deeper procedures.

EMLA has been extensively used in children for a variety of invasive procedures including venipuncture/IV insertion, subcutaneous venous reservoir accessing, lumbar puncture, bone marrow aspiration, laser therapy of dermal lesions, joint aspiration, circumcision, cardiac catheterization and central venous catheter placement [69, 71, 72]. EMLA may be particularly useful in patients undergoing repeated procedures, such as those with oncologic diagnoses, as procedure-related anxiety and needle-phobia can become severe in these patients. It is becoming common practice to have the parents apply the EMLA at home before coming to clinic, thereby avoiding delays while waiting for the cream to be effective.

Reported complications from EMLA are rare. The most serious is methemoglobinemia, which is induced by prilocaine. This is most common in infants as methemoglobin reductase, which converts methemoglobin back to hemoglobin may be deficient in this population[72]. Additionally, fetal hemoglobin is more susceptible to oxidant stresses and therefore more likely to be converted to methemoglobin. Therefore, EMLA cream should be used cautiously in infants under one month of age, and avoided in patients with congential or idiopathic methemoglobinemia, or infants under 12 months of age who are receiving treatment with methemoglobin-inducing agents. Other reported complications have resulted from inadvertent ingestion, usually

from young children picking at the dressing and licking the cream, resulting in airway anesthesia and loss of airway protective reflexes[74]. While serum drug levels should be low if the cream is properly applied, young children should be closely observed to prevent such accidental ingestions and pre-hospital application of EMLA should be avoided.

One of the major drawbacks of EMLA is the time required for it to be effective. This limits it's usefulness in procedures that must be performed semi-urgently and deprives certain children of it's benefits. Newer topical anesthetic formulations including a 4% tetracaine gel, with or without lidocaine, and ELA-Max, a 4% liposomal lidocaine mixture, have a more rapid onset of action and may allow more widespread use of topical anesthetics. Bishai et al performed a cross-over comparison of tetracaine gel with EMLA for Port-a-cath puncture in 39 children and reported equivalent analgesia after only 30 minutes of tetracaine application compared with 60 minutes of EMLA[75]. Similarly, Eichenfield et al reported equivalent pain relief during venipuncture after a 30 minute application of ELA-Max compared to a 60 minute application of EMLA in 120 children[76]. No significant adverse effects have been reported with either preparation.

TAC is a topically applied mixture of tetracaine, adrenaline, and cocaine. Its major application has been for the control of pain associated with laceration suturing in the Emergency Department. Multiple reports have confirmed the safety and efficacy of TAC when used appropriately[77,78]. Contact with mucosal surfaces is to be strictly avoided as significant absorption across these surfaces can occur rapidly. Dosages should be based on both the patients weight and the concentrations of cocaine and tetracaine in the solution as considerable inter-institutional variation exists. Since both

cocaine and epinephrine are vasoconstrictors, TAC should not be applied to areas with limited circulation such as the pinna of the ear, penis, or digits.

Significant toxicity, related to the absorption of cocaine, can occur, especially when TAC is inappropriately applied to mucosal surfaces. Serious complications from such applications have been reported including seizures, respiratory distress, and death[79]. While these events were reported with direct application to mucosal surfaces, inadvertent mucosal absorption from solution dripping or running off of a non-mucosal wound must also be watched for. Newer formulations with a lower cocaine content appear to be efficacious, as do non-cocaine containing solutions[80], which should help limit toxicity.

Superficial and deep infiltration with local anesthetic solutions can also provide effective analgesia during invasive procedures. As systemic toxicity can occur with all agents, limiting the injection on a mg/kg basis is necessary. This is especially important in smaller patients or if the area to be infiltrated is large.

Most practitioners are familiar with the use of lidocaine for topical anesthesia. Use of the 0.5% preparation is suggested as toxic doses are reached more quickly with higher concentrations. The total dose should not exceed 5 mg/kg or 1 ml/kg of the 0.5% solution. The injection of the lidocaine can be painful due to it's acidity (pH = 5.0). Measures to decrease this discomfort include slow injection, use of small gauge needles (27 or 30 Ga), and buffering with the addition of 0.1 to 0.2 mEq of sodium bicarbonate per mL of lidocaine[82]. Alternatively, chloroprocaine, a local anesthetic of the ester class, can be used. Vials of chloroprocaine have a pH close to 7.0, thereby obviating the need of adding sodium bicarbonate. If the drug is carefully and slowly

infiltrated after the application of EMLA cream, it is frequently possible to anesthetize the area without causing any discomfort to the patient.

NONPHARMACOLOGIC METHODS

Nonpharmacologic methods may be used either alone or as an adjunct to pharmacologic treatment. Distraction techniques along with appropriate preparation can significantly influence the amount of sedation required. Preparation can be as simple as informing the child of the intended procedure and the steps involved. This may be done by the treating physician or with the aid of Child Life specialists. These methods have been discussed in greater detail in Chapter ___.

CONCLUSION

With increasing recognition of the importance of adequate procedural comfort measures and the availability of safe and effective agents with which to provide these measures, there are no longer excuses for subjecting children to painful procedures without adequate sedation and analgesia.   Conversely, with growing recognition of the factors associated with adverse sedation outcomes, it is incumbent on all practitioners to ensure that children be sedated in the safest environment possible, meaning conformance with standards prescribed by the AAP and ASA. Despite extensive experience with procedural sedation, pediatric literature regarding various regimens remains limited. Future directions in pediatric procedural sedation should include the development of multicenter collaborative groups to better document the effectiveness of specific agents/regimens, and the components of particularly safe practices.

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Table 1 – Components of the Presedation Assessment

Patients name, age weight and gender
Past medical history
      Underlying medical conditions
      Previous sedation/anesthetic history or problems
Allergies
Current medications
Family history of anesthetic complications
Dietary history (NPO status)
Pregnancy history
Physical examination
      Baseline vital signs, including room air saturation
      Airway examination
      Cardiorespiratory examination
Laboratory (if appropriate)
Summary
      ASA status
      Plan
      Risks discussed

NPO, nil per os (nothing by mouth); *ASA*, American Society of Anesthesiologists.

Table 2 - American Society of Anesthesiology (ASA) Classification System

ASA Class	Description
1	No Underlying Medical Problems
2	Mild Systemic Illness Well controlled asthma, Corrected CHD
3	Severe Systemic Illness Sickle Cell Disease, Severe asthma, Uncorrected CHD
4	Severe Systemic Illness that Is a constant threat to life Uncorrected cyanotic CHD
5	Patient is unlikely to survive 24 hours with or without the procedure

CHD – congenital heart disease

Table 3 – Guidelines for NPO Status prior to elective procedural sedations

Age	Solids/non-clear Liquids	Clear Liquids*
<6 mos	4-6 hrs	2 hrs
6-36 mos	6 hrs	2-3 hrs
>36 mos	6-8 hrs	2-3 hrs
Adults	6-8 hrs or nothing after midnight	2-3 hrs

* Breast milk is considered a clear fluid, formula a non-clear fluid .

Table 4. Suggested Emergency Equipment and Medications for Procedural Sedation

Equipment:

Airway:
       Oral and Nasal Airways - infant, child, small, medium and large adult
       Nasal cannula – infant, child, and adult sized
       Face Masks - infant, child, small adult, medium adult, large adult
       Self-inflating bag-valve set – 250 ml, 500 ml, 1000 ml
       Laryngoscope handles (tested)
       Laryngoscope blades (bulbs tested)
           Miller (Straight) – sizes 0,1,2,3
           Macintosh (Curved) – sizes 1,2,3
       Endotracheal Tubes -   Uncuffed (2.5, 3.0, 3.5, 4.0, 4.5, 5.0 mmID)
                      - Cuffed (5.0, 5.5, 6.0, 6.5, 7.0, 8.0 mmID)
       Stylets – appropriately sized for endotracheal tubes
       Suction catheters – appropriately sized for endotracheal tubes
       Yankauer suction system and nasogastric tubes
       Surgical lubricant
       McGill forceps (optional)

Intravenous equipment:
       Surgical Gloves
       Tourniquets
       Alcohol Swabs
       Adhesive tape, Steri-strips, and Tegaderm
       Arm Boards – small and medium sized
       Sterile gauze (2X2 or 4X4)
       Syringes: 60mL, 10 mL, 5 mL 3 mL, 1 mL
       Needles: 18-, 20-,22, 25 gauge
       Intravenous catheters 18-, 20-, 22-, 24-gauge
       Intraosseus/Bone marrow needle
       Tubing/connectors including T-connectors, 3-way stopcocks, extension tubing (standard, microbore, and burette-type)
       Isotonic intravenous Fluids – Lactated Ringer's or Normal Saline

Medications:
       Oxygen
       Albuterol
       Atropine
       Calcium (chloride or gluconate) – 10% solution
       Dextrose – 50%
       Diphenhydramine HCl
       Diazepam or lorazepam
       Dopamine

Epinephrine – 1:1000 and 1:10,000
Flumazenil
Glycopyrrolate
Hydrocortisone or methylprednisone or dexamethasone
Labetalol
Lidocaine (1 or 2%)
Naloxone
Phenylephrine
Racemic or l-epinephrine for nebulization
Rocuronium or vecuronium
Sodium bicarbonate (0.5 and 1 mEq/mL)
Succinylcholine

Note – choice of specific emergency drugs in various classes may vary according to individual preference, need, and/or availability.

Monitoring Equipment:
Precordial stethoscopes
ECG pads
Blood pressure cuffs
Pulse oximetry probes
End-tidal CO_2 device with sampling tubing

Table 5: University of Michigan Sedation Scale

Score	Sedation Level
0	Fully awake and alert
1	Lightly sedated – appropriate response to verbal conversation and/or sound
2	Sedated – easily aroused with light tactile stimulus or simple verbal command
3	Deeply sedated – aroused only with significant physical stimulation
4	Unarousable

Table 6: Recommended Discharge Criteria

1 – Satisfactory and stable cardiovascular function and airway patency

2 – Patient is easily arousable and protective reflexes are intact

3 – Patient can talk (if age appropriate)

4 – Patient can sit up unaided (if age appropriate)

5 – Patient's level of responsiveness is near normal or as close to normal as possible in

    the pre or non-verbal patient

6 – Patient's state of hydration is adequate.

Table 7: Procedures commonly requiring sedation in Children

Non-invasive	Invasive/Painful

Radiologic
    MRI
    CT Scan
    Nuclear Medicine
Brainstem Auditory Evoked Response
Electroencephalogram
	Lumbar Puncture
	Bone Marrow Aspirate/Biopsy
	Flexible Fiberoptic Bronchoscopy
	Gastrointestinal Endoscopy
	    Gastroduodenoscopy
	    Colonoscopy
	Botulinum Toxin Injections
	Electromyelogram/nerve conduction studies
	Vascular Access
	    Central Venous catheter insertion
	    Arterial Line Insertion
	Thoracentesis
	Thoracostomy tube insertion

Table 8. Procedural Sedation Agents, Doses, and Indications.

Agent	Route	Dose	Indications/Applications
Chloral Hydrate	PO/PR	50-100 mg/kg	Non-invasive radiologic BAER EEG
Midazolam	IV PO IN/SL	0.05-0.1 mg/kg 0.5-0.7 mg/kg 0.2-0.4 mg/kg	Non-invasive radiologic Analgesia for painful procedures
Dexmedetomidine	IV	Induction -0.5-1.0 ug/kg over 10 min, Maintenance - 0.5-0.7 ug/kg/hr	Non-invasive radiologic BAER EEG
Morphine*	IV	0.05-0.15 mg/kg	Short, less painful procedures (e.g. LP, EMG, Thoracentesis)
Fentanyl*	IV TM	1-2 ug/kg 10-20 ug/kg	Short, less painful procedures (e.g. LP, EMG, Thoracentesis)
Remifentanil*	IV	Infusion – 0.05-0.1 ug/kg/min	Short painful procedures Flexible Broncopscopy
Ketamine*	IV IM PO	0.5-1.0 mg/kg 4-6 mg/kg 10 mg/kg	Short radiologic procedures Very Painful procedures Central Venous Catheter Bronchoscopy GI Endoscopy
Methohexital	PR IV	20-30 mg/kg 0.75-1.0 mg/kg	Non-invasive radiologic Short radiologic (i.e. CT scan)
Thiopental	PR	25-50 mg/kg	Non-invasive radiologic
Propofol	IV	1-2 mg/kg q2-3 min	Non-invasive radiologic Analgesia adjunct for painful procedures Bronchoscopy GI Endoscopy
Nitrous Oxide	Inhalation	30-70% with oxygen	Dental procedures Short painful procedures (i.e. burn, laceration).
Lytic Cocktail** (2:1:1 M:P:C)	IM	2 mg/kg meperidine	Invasive radiologic

*Often combined with a sedative (midazolam, propofol).
** No longer recommended; M:P:C: - Meperidine:promethazine:chlorpromazine
IN – Intranasal; SL - Sublingual
BAER – Brainstem Auditory Evoked Response; EEG – Electroencephalogram; EMG – Electromyelogram;
GI – Gastrointestinal