Procedural sedation: A review of sedative agents, monitoring, and management of complications

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ABSTRACT

Given the continued increase in the complexity of invasive and noninvasive procedures, healthcare practitioners are faced with a larger number of patients requiring procedural sedation. Effective sedation and analgesia during procedures not only provides relief of suffering, but also frequently facilitates the successful and timely completion of the procedure. However, any of the agents used for sedation and/or analgesia may result in adverse effects. These adverse effects most often affect upper airway patency, ventilatory function or the cardiovascular system. This manuscript reviews the pharmacology of the most commonly used agents for sedation and outlines their primary effects on respiratory and cardiovascular function. Suggested guidelines for the avoidance of adverse effects through appropriate pre-sedation evaluation, early identification of changes in respiratory and cardiovascular function, and their treatment are outlined.

Key words: *Dexmedetomidine, ketamine, procedural sedation, propofol, respiratory depression*

INTRODUCTION

The greatest threat to the safety of a sedated patient is airway compromise and/or respiratory arrest. To decrease the risk of airway and respiratory complications, careful attention must be directed toward the appropriate selection of medications, adherence to dosing recommendations, and most importantly the identification of the high-risk patient. Regardless of the clinical scenario or the medications used, appropriate monitoring of the patient's respiratory and physiologic functions is mandatory to rapidly identify respiratory compromise. As intervention may be necessary, immediate access to appropriate medications and equipment should be assured. In anticipation of respiratory adverse events, appropriate preparation and monitoring may help detect respiratory depression or upper airway obstruction and allow the opportunity for intervention to prevent further morbidity or mortality.

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Adverse effects on hemodynamic and/or respiratory function may occur whenever sedative and analgesic agents are administered. No agent is devoid of the potential for life-threatening effects on respiratory and hemodynamic function. Malviya *et al.* prospectively evaluated adverse respiratory events in a total of 1140 children, the majority of whom (75%) had received only chloral hydrate.[1] Of the 1140 children, 239 (20.1%) experienced adverse events including inadequate sedation in 150 (13.2%) and a decrease of the oxygen saturation to less than 90% in 63 (5.5%). Five of these children experienced airway obstruction and two became apneic. No adverse event resulted in long-term sequelae. Of the 854 children who received chloral hydrate, 46 (5.4%) experienced decreased oxygen saturation. Children who experienced desaturation after the use of chloral hydrate had received doses (38–83 mg/kg) within the commonly recommended dosing range. In this study, an increased risk for sedation-related adverse events was found in patients deemed American Society of Anaesthesiologist (ASA) physical status III or IV as well as those children less than 1 year of age.

Similar results were reported in a retrospective review of propofol sedation for 251 procedures in 115 pediatric patients.[2] Although propofol resulted in a rapid recovery time (mean of 28.8 minutes) and a 98% success rate, adverse hemodynamic and respiratory effects were noted. Hypotension occurred in 50% of patients with

a systolic blood pressure decrease of 25±12% from baseline. Sixty-one percent of these patients received fluid administration to treat the hypotension. Respiratory depression, requiring bag-valve-mask ventilation, occurred in 15 (6%) of the patients. As demonstrated by these studies and others, potentially life-threatening adverse effects on respiratory and hemodynamic function may occur with any sedative agent used for procedural sedation, including opioids, benzodiazepines, barbiturates, and ketamine.[3,4]

Practitioners providing procedural sedation should have a thorough knowledge of the pharmacology of the agents used. Potential adverse effects of these agents on airway patency, respiratory function, and hemodynamic balance should be fully appreciated. Adverse events during procedural sedation may be prevented by the appropriate pre-sedation evaluation of the patient, intraprocedural monitoring of physiologic function, and early intervention when adverse effects are recognized.

ADVERSE EFFECTS OF SEDATIVE AND ANALGESIC AGENTS

Opioids

The opioids exert their physiologic effects through interactions with receptors that are distributed throughout the central and peripheral nervous system.[5] Respiratory depression may occur with any opioid. The risk of respiratory related complications is dose-dependent and directly related to the potency of the opioid chosen. The opioids are equally capable of leading to respiratory depression when administered in equipotent doses. Respiratory depression from the opioids results from their effects on the respiratory centers in the brainstem. These effects include decreased ventilatory drive related to a reduction of the sensitivity of the respiratory center to hypercarbia and hypoxia. Opioids also interact with respiratory centers in the medulla and pons which regulate the rhythm of breathing. The effects in these areas lead to a decrease in the respiratory rate, followed by a dose-dependent decrease in tidal volume. The effect on ventilatory function is reflected by dose-dependent hypercarbia, hypoxemia and finally apnea with increasing doses. Another factor that must be considered in the setting of procedural sedation is that opioids are frequently administered with a range of sedative drugs including benzodiazepines, phenothiazines, barbiturates, and propofol. Opioids in combination with these agents have a synergistic effect on respiratory function, thereby significantly increasing the risk of hypoventilation, desaturation events, and apnea.[6,7]

In addition to the centrally mediated effects on ventilation, another respiratory effect of opioids is chest wall rigidity.

This phenomenon has been reported with the synthetic opioids including fentanyl, sufentanil, and most recently, remifentanil.[8] It is more common with large doses, rapid administration, and perhaps in younger patients (neonates and infants).[8,9] The spectrum of the clinical manifestations varies from mild coughing following administration to severe chest wall and laryngeal rigidity which impairs ventilation. It is postulated that this effect is mediated in part by the modulation of gamma-aminobutyric acid (GABA) pathways at the spinal cord and basal ganglia levels via fentanyl binding to μ_1 and κ opioid receptors. Other opioids (morphine, meperidine) also bind to these receptors, but have not been reported to cause chest wall rigidity.

Chest wall rigidity has been noted in adults after they receive bolus administration of large doses of fentanyl (50 µg/kg) during anesthetic induction. It has also been reported in both term and preterm neonates at much lower doses (1–2 µg/kg).[8,9] In the series reported by Fahnenstich et al.,[8] with doses of 3–5 µg/kg, the authors noted chest wall rigidity followed by hypercapnia, hypoxemia, and then bradycardia. In two of the patients, endotracheal intubation was impossible due to laryngospasm. Chest wall rigidity was reversed in less than 1 minute by the administration of naloxone (20–40 µg/kg). Although more common with higher doses, both Fahnenstich et al. and Muller and Vogtman reported problems in patients who had received only 2 µg/kg.[8,9] These examples suggest that in neonates, it is particularly important to adhere to dosing guidelines recommending that these drugs be administered slowly and in small increments while titrating to effect. Naloxone should be readily available. As it may take as long as 1 minute for naloxone to reverse chest wall and laryngeal rigidity, airway management equipment (see below) and neuromuscular blocking agents should also be immediately available in case severe hypoxemia and the inability to ventilate are not immediately reversed by naloxone administration.

Meperidine (Demerol) is unique among the opioids in having a relatively high incidence of central nervous system (CNS) side effects.[10] This is due primarily to meperidine's principal metabolite, normeperidine, which can cause tremors, muscle twitches, hyperactive reflexes and seizures. Dysphoria and other CNS effects may result from the parent compound as well. These effects are more likely after prolonged administration of meperidine, with the use of large doses, or in the setting of renal failure or renal insufficiency as the metabolite, normeperidine, is renally excreted. Additionally, anticonvulsant medications such as phenytoin and phenobarbital stimulate hepatic microsomal enzymes which metabolize meperidine to normeperidine. Concomitant use of other medications such as phenothiazines that lower the seizure threshold

may also increase CNS effects related to meperidine. Despite these issues, meperidine continues to be used in the arena of procedural sedation, given the misconception that it is less likely to cause respiratory depression than other opioids. Although CNS effects are more common with meperidine, they have also been reported with other opioids including morphine, fentanyl, alfentanil, and remifentanil.[11-14] As with chest wall rigidity, the CNS effects are thought to be related to excitation of pyramidal neurons of the hippocampus due to inhibition of interneurons of the GABA system.

Opioids differ in their hemodynamic effects. Morphine can cause venodilation as well as histamine release.[15] Historically, the venodilatory effects of morphine have been used in adults with heart failure and pulmonary edema as a means of reducing venous return (preload), thereby resulting in a decrease in left ventricular end-diastolic volume and pulmonary congestion. Despite these vascular effects, morphine is usually not accompanied by a significant change in cardiac output, except in patients who are hypovolemic or in an upright posture. Although other opioids by themselves rarely cause hypotension, all opioids may cause hypotension when used in combination with other sedative drugs, especially propofol or benzodiazepines. This effect is exaggerated in hypovolemic patients.

Additional cardiovascular effects of the opioids may be neurologically mediated. Opioid receptors are widely distributed throughout the central and peripheral nervous system and the hemodynamic effects may be related to binding with receptors in multiple areas in the brain stem (nucleus solitarius and nucleus ambiguus), periaqueductal gray matter, and in the periphery of the sympathetic nervous system.[16] The synthetic opioids also modulate the stress response through receptor-mediated actions on the hypothalamic–pituitary–adrenal axis, thereby decreasing endogenous catecholamine release during procedures. Most opioids reduce sympathetic output and enhance vagal and parasympathetic tone. If not countered by indirect effects (e.g., catecholamine release) or the co-administration of drugs with anticholinergic or sympathomimetic activity (atropine or ephedrine), the synthetic opioids can result in bradycardia and hypotension.[16] Patients who are volume depleted or individuals depending on high sympathetic tone or exogenous catecholamines to maintain cardiovascular function (such as those with heart failure) are predisposed to hypotension. Meperidine, alone among opioids, may cause tachycardia and arrhythmias. These effects may be due to both vagolytic and central stimulant actions. Tachycardia after meperidine administration may be related to its structural similarity to atropine, to normeperidine, its principal metabolite, or to its CNS stimulatory effects.

Propofol

Propofol (2,6-di-isoprophylphenol) is commonly classified as an intravenous anesthetic agent. Because of its insolubility in water, it is commercially available in an egg lecithin emulsion as a 1% (10 mg/mL) solution. Its chemical structure is distinct from that of the barbiturates and other commonly used anesthetic induction agents. Propofol is a sedative/amnestic agent, possesses no analgesic properties, and should be combined with an opioid or ketamine (commonly known as "ketofol") when analgesia is required. Like the barbiturates (see below), its effects are mediated through the GABA receptor system by increasing chloride conductance across the cell membrane. The anesthetic induction dose of propofol in healthy adults ranges from 1.5 to 3 mg/kg with recommended maintenance infusion rates varying from 50 to 200 µg/kg/minute (3–6 mg/kg/h), depending on the depth of sedation that is required. Following intravenous administration, propofol is rapidly cleared from the central compartment and undergoes hepatic metabolism to inactive water-soluble metabolites, which are then renally cleared. Its rapid redistribution, clearance, and metabolism provide rapid awakening when the infusion is discontinued. Rapid arousal and quick return to baseline behavior allows for early discharge following outpatient procedures.

Although initially introduced for anesthetic induction and maintenance, propofol's pharmacodynamic profile including a rapid onset, rapid recovery time, and lack of active metabolites has accounted for its popularity in the arena of procedural sedation.[2,17,18] In addition to its favorable properties with regard to sedation and recovery times, propofol has beneficial effects on CNS dynamics, including a decreased cerebral metabolic rate for oxygen ($CMRO_2$), cerebral vasoconstriction, and lowering of intracranial pressure (ICP).[19,20] These effects are clinically similar to those seen with the barbiturates and etomidate (see below). Given these effects, propofol may be an effective and beneficial agent for sedation in patients with altered intracranial compliance due to traumatic brain injury, provided that the patient is receiving ventilatory support to prevent increases in $PaCO_2$ related to the respiratory depressant properties of propofol (see below).

Like many of the sedative/analgesic agents, propofol has significant respiratory depressant effects, which may be exacerbated by its combination with other agents (e.g., opioids). Propofol shifts the CO_2 response curve to the right, but unlike the opioids, does not depress the slope. A similar effect is seen with the administration of barbiturates or benzodiazepines. Reports regarding the use of propofol for procedural sedation in spontaneously breathing patients demonstrate a high incidence of respiratory effects including hypoventilation, upper airway

obstruction, and apnea.[2] Clinically significant respiratory effects include upper airway obstruction due to effects on upper airway (pharyngeal) musculature, hypoventilation with hypercarbia, hypoxemia, and/or apnea. These effects are dose dependent and more likely with higher doses as deeper levels of sedation/anesthesia are achieved. There is significant interpatient variability regarding the dose required to induce any of these adverse respiratory events.

Propofol decreases mean arterial pressure (MAP) related to both peripheral vasodilation and negative inotropic properties.[21] Propofol alters baroreflex responses, resulting in a smaller increase in heart rate for a given decrease in blood pressure. These cardiovascular effects are especially pronounced following bolus administration. Although well tolerated by patients with adequate cardiovascular function, these effects may result in detrimental physiologic effects in patients with compromised cardiovascular function. The adverse hemodynamic effects may be mitigated with normal saline fluid boluses (20 mL/kg) or by the administration of calcium chloride (10 mg/kg).[22] Such treatment is rarely necessary, except in patients with co-morbid diseases (traumatic brain injury) in whom the decrease in blood pressure may not be desirable due to concerns of decreasing cerebral perfusion pressure. In the relatively healthy patient undergoing procedural sedation, the administration of calcium chloride or fluid boluses is generally not necessary. In fact, in specific circumstances, such as when sedating for nuclear medicine, excessive fluid administration may cause the patient to void into their diaper which may either cause the child to awaken/move during the study or lead to the accumulation of the isotope in the diaper, thereby affecting interpretation of the study.

Additional cardiovascular effects relate to propofol's augmentation of central vagal tone leading with the potential for bradycardia or even asystole when combined with other medications that decrease cardiac chronotropic function (fentanyl, succinylcholine).[23,24] Given the potential for respiratory and hemodynamic effects, although generally safe and effective when used by practitioners with advanced airway training and experience in procedural sedation, appropriate monitoring (see below) and ready access to equipment for emergency airway management and cardiovascular resuscitation is mandatory.

Ketamine

Ketamine is the only dissociative anesthetic agent currently in clinical use. It is structurally related to the street hallucinogen phencyclidine (PCP). Unique features of ketamine, which make it particularly attractive for procedural sedation, include the provision of amnesia, sedation, immobilization and profound analgesia along with limited deleterious effects on hemodynamic and respiratory function. These characteristics allow for the completion of short, painful procedures such as fracture reduction, abscess incision and drainage, burn debridement, or cosmetic repair of complex facial lacerations following dog bites under optimal conditions. Fortuitously, ketamine has also been shown to be a valuable agent for procedural sedation in combative patients, mentally disabled patients or autistic patients.[25]

Ketamine's anesthetic and analgesic properties result from poorly defined mechanisms within the limbic and thalamic systems, providing what has been termed "dissociative anesthesia".[26] This is a unique state which prevents higher centers in the brain from perceiving visual, auditory and painful stimuli. The condition is often described as "the lights are on, but no one is home". Ketamine is commercially available as a racemic mixture of two isomers in concentrations of 10 mg/mL (1%), 50 mg/mL (5%) or 100 mg/mL (10%). Considering the ready availability of these various concentrations, extreme caution is required when preparing the medication for administration so as not to confuse the more concentrated solution [ideal for intramuscular (IM) administration as less volume is indicated] with the more dilute solution thus resulting in a potential overdose with intravenous administration.

Ketamine has a rapid onset (less than 5 minutes) when administered via the intravenous or IM routes, with a recovery time averaging between 45 and 120 minutes. Typically, at an intravenous dose of 1–1.5 mg/kg or an IM dose of 2–4 mg/kg, the patient will enter into a trance-like state with the characteristic dissociative features. This state cannot be "deepened" by further dosing. Ketamine "titration" would more aptly be used to describe redosing with smaller aliquots (0.5 mg/kg) to maintain the patient in a trance-like state in order to successfully complete longer procedures. Ketamine is metabolized primarily by hepatic N-methylation to various metabolites including norketamine, which is further metabolized and ultimately excreted in the urine. Norketamine retains one-third of the analgesic and sedative properties of the parent compound. Given its dependence on hepatic metabolism, infusion parameters or repeat doses should be reduced in patients with hepatic dysfunction. The bioavailability of ketamine is 100% following intravenous or IM administration, but is markedly decreased with oral or rectal administration (making these modes of drug administration less reliable) because of limited absorption and a high degree of first-pass hepatic metabolism. Formation of norketamine during first-pass metabolism may account for a significant part of the anesthetic effect following oral or rectal administration.

Ketamine maintains cardiovascular function and has limited effects on respiratory mechanics. In the majority

of clinical scenarios, ketamine results in a dose-related increase in heart rate and blood pressure, mediated through the sympathetic nervous system with the release of endogenous catecholamines.[27-30] These effects are generally seen even in patients with congenital heart disease where reports have demonstrated a stable or increased oxygen saturation in patients with cyanotic lesions.[31] Ketamine's positive inotropic effects, increased heart rate, and increased blood pressure may result in a concomitant increase in myocardial oxygen consumption. This effect can alter the balance between myocardial oxygen demand and delivery, inducing ischemia in patients with ischemic heart disease (a rare event in the pediatric population). Ketamine-induced hypertension and tachycardia can be decreased by the administration of ketamine with a benzodiazapine, a barbiturate, propofol, or a synthetic opioid. Although ketamine's indirect sympathomimetic effects generally overshadow its direct negative inotropic properties, hypotension and even cardiac arrest may occur in patients with diminished myocardial contractility. In these patients, ketamine's direct negative inotropic properties predominate because the endogenous catecholamine stores have been depleted.

Functional residual capacity, minute ventilation, and tidal volume remain unchanged following ketamine administration.[32] In an animal model of reactive airway disease, Hirshman *et al.* demonstrated improved pulmonary compliance, decreased resistance, and prevention of bronchospasm after ketamine administration.[33] These factors have made ketamine a popular sedative choice when rapid sequence intubation is necessary in asthmatic patients. The effects on respiratory mechanisms have been partially attributed to effects from the release of endogenous catecholamines.[33] Although minute ventilation is generally maintained, hypercarbia and a depressed ventilatory response to CO_2 may occur.[34,35] Although clinical use and experimental studies suggest that airway reflexes are maintained, aspiration and laryngospasm have been reported following ketamine administration in spontaneously breathing patients without a protected airway.[36,37] Such adverse events have been suggested to be more common when the medication is administered rapidly, thereby resulting in the recommendations that the intravenous bolus dose be administered over 1–2 minutes.[37] These adverse respiratory events, although rare, may occur more commonly with IM administration.[38]

Ketamine can cause apnea, especially in higher doses, when combined with other sedative/analgesic agents, or in critically ill patients. There is an associated increased risk of adverse respiratory events with ketamine use in children less than 3 months of age. This is attributable to differences in airway anatomy and laryngeal excitability seen in this age group. Thus, ketamine use for procedural sedation is relatively contraindicated in children less than 3 months of age and should be used with additional caution in children 3–12 months of age.

When considering ketamine as the potential sedative in the sedation plan, it is essential to be aware of contraindications that may lead to an increased likelihood of an adverse event. These relative and absolute contraindications include age less than 3 months, a history of airway instability, procedures involving the posterior pharynx, acute pulmonary infections, acute ocular globe injuries, patients with known psychotic diagnosis (schizophrenia), severe cardiovascular disease (congestive heart failure or hypertension) and head injury with signs of increased ICP. The latter relative contraindication is currently undergoing significant controversy as the potential for ketamine to acutely increase ICP has recently been refuted with additional evidence demonstrating a potential neuroprotective effect.[39] Ketamine may also increase oral secretions which can then influence airway patency and further compromise respiratory function. This effect is mediated via stimulation of central cholinergic receptors. To lessen such problems, an anti-sialogogue such as atropine (0.01 mg/kg, minimum dose of 0.1 mg with a maximum dose of 0.4 mg) or glycopyrrolate (0.005 mg/kg, maximum dose of 0.2 mg) has been traditionally administered prior to or along with ketamine. This latter practice is also in evolution, as the recent literature suggests that routine use of atropine premedication may not be necessary.[40] If atropine is chosen as an adjunctive agent for IM administration, it may be combined in the same syringe with ketamine and even midazolam to allow for a single injection.

In routine clinical use, ketamine is also commonly administered with the benzodiazepine, midazolam, to blunt the associated emergence phenomena (hallucinations and dreaming). However, recent studies suggest that routine use of adjunctive midazolam with ketamine does not effectively reduce the incidence of these emergence phenomena.[41] With the addition of midazolam to ketamine for procedural sedation, there was a statistically significant increase in recovery times as well as an increased risk for adverse respiratory events. The only positive attribute was a reduction in the incidence of emesis during the recovery period.

Considering some of ketamine's unique characteristics, specific techniques for preparing the sedation environment may lead to a better experience for the patient, their families and the staff. We would suggest the education of parents regarding what they should expect to see (open eyes with nystagmus, aimless stare) in their child while in the dissociative state as this may be disconcerting if they

are not properly prepared. Having older children plan in advance pleasant topics to dream about may decrease the incidence of unpleasant emergence phenomenon. Similar efforts should be made during induction and recovery to reduce stimuli to the patient. This may include closing doors, turning the lights down in the room, keeping the room quiet, and decreasing physical contact with the patient to reduce the likelihood of agitation upon awakening. Parents, although well intentioned, need to be told not to stimulate their child prematurely.

Etomidate

Etomidate is a carboxylated imidazole-ring containing intravenous anesthetic agent which was introduced into clinical anesthesia practice in 1972. The aqueous solution of etomidate is available as a 0.2% (20 mg/mL) solution with the carrier vehicle, propylene glycol. A pH of 6.9 of this combination accounts for pain and the potential for the development of thrombophlebitis when administered via a peripheral vein. As with other medications that contain propylene glycol as a diluent (lorazepam), although one-time administration is not a problem, toxicity has been reported following long-term infusions.[42]

Etomidate's mechanism of action is via the GABA system, with alterations of chloride conductance across the cell membrane.[43] Etomidate's popularity in anesthetic practice lies in its limited effects on cardiovascular and hemodynamic function even in patients with co-morbid diseases, as compared with other intravenous anesthetic agents (propofol and the barbiturates).[44,45] Anesthetic induction doses of 0.2–0.3 mg/kg provide a rapid onset of amnesia and sedation with rapid emergence. Etomidate undergoes hepatic ester hydrolysis with the formation of inactive water-soluble metabolites, thus the elimination half-life is prolonged in the setting of hepatic dysfunction. As etomidate possesses limited analgesic properties, the concomitant administration of a synthetic opioid is frequently used in anesthetic practice to provide more reliable analgesia from painful stimuli including endotracheal intubation. Similar to the barbiturates and propofol, etomidate decreases the cerebral metabolic rate for oxygen ($CMRO_2$), resulting in cerebral vasoconstriction and a decrease in cerebral blood flow (CBF) and ICP. Given its limited effects on cardiovascular function, cerebral perfusion pressure (CPP) is maintained. These properties have led to its popularity for anesthetic induction and emergency airway management in patients with altered myocardial contractility and increased ICP.

The most significant concern regarding etomidate and the one causing its decreased use recently is an effect on the endogenous production of corticosteroids. These effects mandate that it not be used as repeated doses or a

continuous infusion for prolonged sedation in the Intensive Care Unit setting.[46] Etomidate inhibits the function of the enzyme, 11-β hydroxylase, which is necessary for the production of cortisol, aldosterone, and corticosterone. Temporary inhibition, lasting 12–24 h, has been shown to occur after even a single dose of etomidate.[47] Although controversial, this effect has led some authorities to caution against the use of even a single dose of etomidate in certain patient populations, particularly those suffering from septic shock. Exposure to single dose etomidate has also been shown to be a modifiable risk factor in trauma patients. Trauma patients receiving single dose etomidate for rapid sequence intubation (RSI) were found to have an increased risk for the development of adrenal insufficiency and ultimately to have poorer outcomes than a similar group who did not receive etomidate.[48] These issues have led to a re-evaluation of the use of etomidate at our institution as part of our RSI protocol for trauma patients. It is likely that etomidate use will discontinue in favor of ketamine for these patients.

Although used commonly as part of a medication regimen for endotracheal intubation, there are limited published data outlining the use of etomidate for other types of procedural sedation. Etomidate has been used to provide sedation during cardioversion, especially in patients with compromised cardiovascular function. In the emergency department setting, etomidate sedation has been utilized for sedation during short, painful procedures such as joint (hip and shoulder) dislocation reduction and fracture management.[49]

Barbiturates

Propofol and the barbiturates are the two most commonly used agents for anesthetic induction during surgical procedures in the operating room. The barbiturates are classified according to their duration of action and their chemical structure. Short-acting barbiturates include methohexital, thiopental, and thiamylal. The short-acting agents have a rapid distribution, and thus a short duration of action of 5–10 minutes following a single bolus dose. If a more prolonged sedative effect is needed, a continuous infusion of these agents is required to maintain plasma concentrations. Care should be taken when used in this fashion as accumulation of the drug throughout the body may occur resulting in a prolonged duration of action when the infusion is discontinued. Pentobarbital is considered an intermediate-acting agent while phenobarbital is a long-acting barbiturate. Given their long history of clinical use and availability, barbiturates remain a popular agent for sedation, particularly during noninvasive radiologic procedures such as computed tomography (CT) or magnetic resonance imaging (MRI). These drugs produce reliable sedation with short induction times and a quick recovery.

However, the barbiturates can have profound effects on ventilatory and cardiovascular function. These effects are generally dose dependent, but may also be altered by interpatient variability as well as the presence of co-morbid diseases. Respiratory effects may result from both alterations in upper airway tone resulting in upper airway obstruction and effects on the central control of ventilation resulting in direct hypoventilation and even apnea. In healthy patients, sedative doses generally can be expected to have minimal effects on respiratory drive and airway protective reflexes, while respiratory depression, apnea, or hypotension may occur with larger doses or with administration to patients having cardiorespiratory compromise. The cardiorespiratory effects are additive when the barbiturates are used with other agents such as opioids. Hypotension results from both peripheral vasodilation with a decrease in preload/afterload and a direct negative inotropic effect. In some cases, barbiturate dosing is associated with a paradoxical reaction associated with restlessness, excitement and delirium. This effect can be reversed with the oral or intravenous administration of caffeine.[50]

Nitrous oxide

Nitrous oxide (N_2O) was synthesized in 1776 by Priestly and its anesthetic properties were demonstrated by Humphrey Davy in 1799. Despite Davy's opinion regarding the potential of this agent for the management of pain, it was not until 1844 that Gardner Colton used nitrous oxide as an anesthetic agent during a tooth extraction. Although used most commonly as part of intraoperative anesthetic care, nitrous oxide has also found applications outside of the operating room in the arena of procedural sedation.[51,52] These applications are likely to increase as two companies are in the process of marketing specific compact machines for the delivery of N_2O in remote areas for procedural sedation.

N_2O has a rapid onset of action, is relatively easy to use and is inexpensive. It provides amnesia, sedation and analgesia. Its effects dissipate rapidly when administration is discontinued. Because of its low blood–gas partition coefficient (relative insolubility in blood), its alveolar concentration rises rapidly, resulting in a rapid onset of action. Nitrous oxide's minimum alveolar concentration or MAC (a measure of anesthetic potency, which describes the anesthetic concentration at which 50% of patients will move in response to surgical incision) is 105%. As this concentration is impossible to achieve at normal barometric pressure, additional agents may be necessary for more painful procedures. In clinical practice, nitrous oxide is administered in concentrations varying from 30 to 70% by a face or nasal mask. Alternatively, a weighted mouthpiece that is held in place by the patient during administration can be used. If the patient becomes excessively sedated, the device falls from the patient, thereby interrupting the administration of nitrous oxide.

As with all of the agents discussed in this review, nitrous oxide should be administered only with standard procedural sedation monitoring. Nitrous oxide delivery devices must employ specific safety features including a monitor of the inspired oxygen concentration, a device that limits the ratio of the flow rates of oxygen to nitrous oxide (a proportioning system so that less than 30% oxygen cannot be administered), and a system that cuts off the nitrous oxide flow if the oxygen supply fails. This eliminates the potential administration of 100% nitrous oxide should an interruption in the oxygen supply occur.

In the operating room, nitrous oxide and oxygen are administered from the wall outlets connected to the hospital's central supply. In other areas where such a supply is not available, nitrous oxide can be administered from E cylinders and mixed with oxygen to provide the desired concentration. Outside the United States, commercially available tanks are manufactured that contain a 50–50 oxygen and nitrous oxide mixture, thereby limiting the risk of a hypoxic mixture and the need for specialized equipment to mix oxygen and nitrous oxide from separate tanks. A scavenger device attached to the delivery system is also required to remove waste gases and prevent environmental pollution. Repeated exposure of the patient or healthcare workers to nitrous oxide can lead to teratogenic effects, increased risk of spontaneous abortion, bone marrow suppression or megaloblastic anemia, and peripheral neuropathy as a result of its effects on B_{12} metabolism and protein synthesis. Because of the potential for abuse and/or illicit use, nitrous oxide tanks should be kept under close surveillance.

Potential respiratory and hemodynamic effects of nitrous oxide include a dose-dependent negative depressant effect on myocardial contractility and increases in pulmonary artery pressure. Nitrous oxide also causes dose-dependent respiratory depression, resulting in an elevation of the resting $PaCO_2$ level and blunting of the central respiratory response to hypercarbia and hypoxemia.[53] These effects may be modified by the co-administration of other agents or the presence of co-morbid diseases. Despite its relative insolubility in blood, during the administration of nitrous oxide, a large amount is taken up into the blood. This latter effect, known as the second gas effect of anesthesia, increases the alveolar PaO_2 resulting in an added margin of safety during induction even if high concentrations of nitrous oxide (80–90%) are administered. Once the administration of nitrous oxide is discontinued, this effect occurs in the opposite direction, resulting in a lowering

of the alveolar P_{O2}, which can result in hypoxemia unless supplemental oxygen is administered until the nitrous oxide is eliminated from the body.

Nitrous oxide has been used successfully for pediatric procedural sedation in the emergency department primarily for orthopedic reductions and laceration repairs, with good patient and parent satisfaction scores. An exciting new avenue in the use of nitrous oxide is its increased use for brief, radiologic procedures. Nurse administered nitrous oxide has been particularly successful in sedating children for urinary catheterization for voiding cystourethrograms.[54] Using well-trained and supervised nurses as sedation providers may ultimately increase children's access to sedation for these brief and yet painful procedures. However, some studies suggest that for particularly painful procedures, nitrous oxide as a sole agent may not be sufficient as high pain scores have been reported when nitrous oxide is used alone. Further studies are needed to assess the efficacy of nitrous oxide combined with other agents for very painful procedures.[55]

Chloral hydrate

Chloral hydrate was originally synthesized in 1832 and introduced into clinical practice in 1869 by Liebreich. For street and recreational use, chloral hydrate is the ingredient combined with alcohol in mixtures known as 'knockout drops" and "Mickey Finns". For clinical use, it is available in several different preparations and concentrations including capsules (250 mg, 500 mg), syrup (250 mg/5 mL and 500 mg/5 mL), and suppositories (325 mg, 500 mg, and 650 mg). Chloral hydrate can be a gastrointestinal (GI) irritant, especially when administered to patients who have been nil per os (NPO), resulting in nausea and vomiting. In younger children, these problems can be avoided with the use of suppositories. Chloral hydrate has no analgesic properties and should be combined with an analgesic agent such as an opioid if analgesia is required.

Chloral hydrate is rapidly absorbed from the GI tract with a bioavailability that approaches 100%. Its onset of action is within 20 minutes, with a peak effect at 30–60 minutes. It undergoes hepatic metabolism by the enzyme, alcohol dehydrogenase, to the active component, trichloroethanol (TCE). TCE is then further metabolized by either glucuronidation or oxidation to inactive metabolites. Less than 10% of chloral hydrate undergoes renal excretion. The plasma half-life of TCE is 8–12 h in children, but may be prolonged up to 24–36 h in neonates and infants.[56,57]

Chloral hydrate and its metabolite TCE are CNS depressants. In therapeutic doses, there are minimal effects on cardiorespiratory function and upper airway control. Apnea and hypotension can occur with excessive dosing or when administered to patients with compromised cardiorespiratory or CNS function. Cardiovascular effects include decreased myocardial contractility, a shortened refractory period, and an altered sensitivity of the myocardium to endogenous catecholamines.[58] The latter two effects account for its pro-arrhythmogenic effects. Chloral hydrate should not be administered to patients with toxic ingestions that may predispose to arrhythmias such as tricyclic antidepressants.[58]

In procedural sedation, chloral hydrate has been primarily used to induce sleep. As it has no analgesic qualities, chloral hydrate should not be employed for sedation for painful procedures. Chloral hydrate's ability to induce sleep has traditionally made it a popular agent for sedation for anxiety producing radiologic procedures such as CT and MRI. It has also been used for non-painful procedures not requiring strict immobility such as electroencephalography (EEG), echocardiography and electrocardiography (ECG). Generally considered one of the safest sedative agents, chloral hydrate does have the potential for causing unexpectedly deep levels of sedation as well as upper airway obstruction in some patients. Adverse events have been reported even when chloral hydrate is administered within acceptable dosing limits. Poor outcomes have also been documented when chloral hydrate is administered by non-medically trained personnel. Despite the universal agreement that it violates the standard of care and acceptable safety standards, some practitioners still prescribe chloral hydrate to be administered at home prior to coming to the hospital for a procedure.[59] As a result of this practice, adverse events have been reported on the way to a facility for a procedure. Additionally, secondary to chloral hydrate's long half-life, some adverse events have also taken place in automobiles or at home after discharge from medical supervision, further mandating the need for appropriate discharge criteria following procedural sedation. As a result of associated morbidity and mortality from chloral hydrate, the American Academy of Pediatrics (AAP) has issued a position paper on the recommended use of this agent which was published in the May 1993 issue of AAP News.

Benzodiazepines

The benzodiazepines bind to receptor sites in the GABA system, increasing the efficacy of the interaction between GABA, its receptor, and the chloride channel. Midazolam (Versed™) is the benzodiazepine most frequently used for procedural sedation. It is a short-acting, water-soluble agent which provides reliable anxiolysis, sedation and amnesia. Of clinical note, the benzodiazepines as a group, provide no analgesia, and so are often co-administered with opioids, generally fentanyl, because of their similar pharmacokinetic profiles (rapid onset and offset), which are desirable

during procedural sedation. Benzodiazepine metabolism occurs via hepatic oxidation and glucuronidation with the potential prolongation of their effects in patients with hepatic dysfunction.

Effective sedation with midazolam can be provided by multiple routes of administration including oral, intranasal, rectal, intramuscular, and intravenous delivery. The benzodiazepines can have adverse effects on respiratory and hemodynamic function. These effects occur in a dose-dependant fashion and are modified by co-morbid diseases and the synergistic effect of co-administration with other sedative/analgesic agents such as the opioids. When midazolam is co-administered with an opioid, the sedation plan should include titration to effect beginning with a lower dose of midazolam (0.05 mg/kg). Other clinically significant adverse effects include paradoxical excitement which may occur in up to 10–15% of patients.[60] These effects can be particularly alarming to family members and staff, as they are completely opposite in nature to the desired and expected results.

Dexmedetomidine

Currently, there is increased interest in the use of dexmedetomidine as an agent for procedural sedation. Dexmedetomidine is an α_2-adrenergic agonist with beneficial sedative properties and a limited adverse effect profile. Both dexmedetomidine and clonidine are imidazole compounds that exhibit a high ratio of specificity for the α_2 versus the α_1 receptor. Clonidine exhibits an $\alpha_2:\alpha_1$ specificity ratio of 200:1 compared to 1600:1 for dexmedetomidine. An additional difference is the half-life of 12–24 h for clonidine and 2–3 hours for dexmedetomidine. Dexmedetomidine causes its physiologic effects by activation of specific transmembrane α_2 adrenergic receptors at various locations throughout the CNS. These effects include sedation, anxiolysis and analgesia. Initial Food and Drug Administration (FDA) approval regarding dexmedetomidine was for the provision of sedation for up to 24 hours in adults requiring mechanical ventilation. More recently, dexmedetomidine received FDA approval for monitored anesthesia care or procedural sedation occurring within the operating room. Although there is growing experience with the use of this agent in the pediatric population, it still does not hold FDA approval for such use.

Dexmedetomidine can have deleterious effects on cardiorespiratory function. In a study of adult patients undergoing vascular surgery, Venn *et al.* reported that 18 of the 66 patients who received dexmedetomidine experienced adverse hemodynamic effects including hypotension (mean arterial pressure ≤60 mmHg or a greater than 30% decrease from baseline) or bradycardia

(heart rate ≤50 beats/minute).[61] In 11 of these patients, the hemodynamic effects were noted during the bolus infusion. Hypertension has also been reported during the loading dose. This hemodynamic effect is thought to be mediated via peripheral α_{2B}-adrenergic agonism leading to vasoconstriction prior to the onset of the central effects. Other investigators have reported the potential for the development of bradycardia with dexmedetomidine although in most cases the blood pressure is well maintained.[62] Bradycardia appears to be more common when dexmedetomidine is co-administered with other medications that have negative chronotropic effects.[63]

The initial clinical trials suggested that the potential for respiratory depression with dexmedetomidine was limited. Hall *et al.* demonstrated sedation, impairment of memory, and decreased psychomotor performance during dexmedetomidine infusions (0.6 µg/kg bolus followed by either 0.2 or 0.6 µg/kg/h) in healthy adult volunteers.[64] No changes were noted in hemodynamic variables or respiratory function [end-tidal CO_2 ($EtCO_2$), oxygen saturation, respiratory rate]. However, other studies have noted a modest increase in $PaCO_2$ values during dexmedetomidine infusions as well as a depression of the slope of the CO_2 response curve and blunting of the ventilatory response to increasing $PaCO_2$ levels in healthy adult volunteers.[65] Additionally, anecdotal reports in both adult and pediatric patients have mentioned rare cases of upper airway obstruction following the administration of dexmedetomidine.

MONITORING TO IDENTIFY ADVERSE RESPIRATORY AND HEMODYNAMIC EVENTS

Given that respiratory and hemodynamic effects may occur with any agent by any route, means to identify such problems are mandatory in all patients who receive procedural sedation. Given the importance of such monitoring in identifying adverse effects of sedative and analgesic agents, several organizations representing pediatrics, anesthesiology and emergency medicine have published procedural sedation guidelines which include sections suggesting appropriate monitoring during and after the administration of such medications.[66-69] The guidelines of the AAP are currently in its third edition, having been modified as new information becomes available since its original publication in 1985. Of equal importance in the monitoring of patients during the procedure is to continue monitoring throughout the recovery phase. Once the stimulus of the painful procedure is completed, apnea or airway obstruction may occur due to the residual effects of the sedative/analgesic agents. Practically, this is particularly relevant, for example, after completion of an orthopedic

reduction when frequently the patient is transported to the Radiology Department for post-reduction films. It is important that diligent monitoring is continued during the transport, while in the Radiology Department, and upon the patient's return to the Emergency Department to monitor for and address the complications that may arise.

The guidelines suggested by these physician organizations recommend 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. The most important component of monitoring during procedural sedation is to have one person whose only job is to sedate and monitor the patient. The practitioner performing the procedure cannot act as both the monitor and sedation provider. As in the operating room, the hemodynamic, respiratory and oxygen saturation monitors are meant as a supplement to the person whose job it is to watch the patient. When feasible, this person should have an unobstructed view of the patient's face, mouth, and chest wall throughout the procedure.

Routine monitoring during procedural sedation should include continuous pulse oximetry and ECG monitoring as well as intermittent recordings of respiratory rate and blood pressure at a frequency of at least every 5 minutes during the procedure. This may be decreased as the patient regains consciousness during the recovery phase. Additionally, some ongoing monitoring of respiratory function is suggested such as observation of the patient's chest moving, use of a precordial stethoscope to auscultate breath sounds or use of an $EtCO_2$ monitor (see below). All these monitors have limitations and the practitioner must be cognizant of these and not rely on the monitors solely to assess the patient's well-being.

Pulse oximetry remains the most widely used monitor during procedural sedation. The currently available oximeters are calibrated for oxygen saturation (SaO_2) values over 80% and lose their accuracy at values less than 75%.[70] In the majority of patients, this is not of clinical significance, given that their SaO_2 values would normally be in the upper 90% range; however, this may become an issue when sedating patients with residual cyanotic congenital heart disease where SaO_2 values of 70–80% are common. Additional issues that may interfere with continuous pulse oximetry readings include patient movement or poor perfusion states. Patient movement may be interpreted as pulsatile flow resulting in inaccurate readings or prohibiting any meaningful measurement of oxygen saturation.[71] To identify such issues, it is recommended that pulse oximeters which display the plethysmography tracing be used. Placement of the oximeter probe on cool extremities

or in patients with decreased peripheral perfusion may also limit the accuracy of pulse oximetry. Finally, there may be a significant delay between the development of hypoxemia and its registration by the pulse oximeter. Many of these issues have been addressed by the newest generation of pulse oximetry technology and by the development of forehead reflectance sensors, which appear to be more rapidly responsive and less sensitive to motion artifact and extremity temperature.[71,72]

Some authorities have begun to recommend the use of continuous $EtCO_2$ monitoring as a way to recognize apnea sooner than it would be detected by pulse oximetry (60–90 second delay). $EtCO_2$ monitoring utilizes infrared technology and the differential absorption or refraction of infrared light by the CO_2 particles in the exhaled gas. This generates a waveform that is displayed with each exhalation. If there is central or obstructive apnea, the waveform immediately extinguishes and the healthcare provider is immediately alerted to the fact that there is no longer gas exchange. Additionally, as the CO_2 content of the expired gas correlates fairly well with arterial CO_2 values, increasing hypercarbia from over-sedation can be recognized. Although initially used only in intubated and mechanically ventilated patients, refinements in the technology have led to the production of specialized nasal cannulae which allow for $EtCO_2$ monitoring in spontaneously breathing patients without an artificial airway. Several clinical studies have demonstrated the early identification of respiratory depression using this technology and have clearly indicated its superiority over pulse oximetry in many clinical scenarios.[73,74]

In addition to monitoring vital signs and cardiorespiratory function, there are also benefits to monitoring the efficacy and depth of the sedation provided. Patient comfort during procedures has become increasingly recognized as a major factor in determining what is considered adequate sedation. As such, the concept of pain as the fifth vital sign continues to gain popularity. Assessment of pain during procedures is somewhat more difficult in pediatric patients, especially in the pre-verbal or non-verbal patient. Whereas scoring systems to assess pain in other arenas (postoperative period) have been well established, the availability and use of such scoring systems remain limited during invasive procedures. Although the lack of movement or response during a painful procedure likely indicates the absence of significant pain, it would be inappropriate and perhaps even dangerous to expect every patient undergoing painful procedures to be sufficiently sedated as to lose all responsiveness. Additionally, the greatest risk to patient safety is not under-sedation, but rather over-sedation. As such, a means of accurately assessing the depth of sedation remains important.

During lighter planes of sedation, the depth of sedation may be assessed by the patient's ability to appropriately respond to questions or verbal stimuli. For deeper levels of sedation, a variety of sedation scales have been developed to better quantify the degree of unconsciousness. Such scales include the Observers' Assessment of Alertness/Sedation (OAAS) scale, the Vancouver Sedative Recovery Scale, and the University of Michigan Sedation Scale (UMSS).[75-77] Although validated in children and adults, each of these scales may have specific drawbacks for use during procedural sedation. The OAAS, although effective in differentiating light from deep sedation, may be less effective in differentiating deeper levels of sedation from each other. The Vancouver Sedative Recovery Scale, although better in differentiating deeper levels of sedation, is too cumbersome to be easily utilized during short procedures. The UMSS was developed to be a simple and an efficient tool to assess the depth of sedation over the entire sedation continuum. It utilizes a simple scale ranging from 0 to 4 (0 being an awake, alert patient and 4 indicating unresponsiveness); and like the other scales, it requires patient stimulation to make an assessment. This technique is not acceptable for many procedures as the goal is to have the patient immobile.

In light of these concerns, the bispectral index (BIS) or other depth of anesthesia monitor may be a valuable adjunct to monitoring during procedural sedation. Originally developed for use in the operating room, the BIS monitor uses a specific algorithm to analyze the modified EEG and thereby assess the hypnotic effects of sedative and anesthetic agents. Based on various features of the EEG, a number is assigned ranging from 0 (isoelectric EEG) to 100 (fully awake). Although validated and used most commonly for intraoperative use, there may be a future role for BIS monitoring during procedural sedation as a means of evaluating the depth of sedation and perhaps avoiding over-sedation and respiratory compromise.

Gill *et al.* compared BIS values with Ramsay sedation scores in 37 adult Emergency Room patients receiving procedural sedation and/or analgesia.[78] The authors reported a significant correlation between BIS and depth of sedation, but noted a wide variability in BIS values at similar sedation scores. The BIS was most effective in 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 years of age.[79] The authors reported a good correlation between BIS value and sedation score, including patients less than 6 months of age. However, they reported that the correlation was somewhat agent dependent. The correlation was less accurate in patients receiving either ketamine or a combination of oral chloral hydrate, hydroxyzine, and meperidine.

More recent information further supports the potential utility of BIS monitoring during procedural sedation. In a prospective study of 86 children undergoing procedural sedation, 35% of patients achieved a BIS value less than 60, indicative of general anesthesia.[80] Additionally, adverse respiratory and airway events were more common in patients with BIS values indicative of deep sedation (61–70) or general anesthesia. Oxygen desaturation occurred in 6 of 41 patients in the deep sedation or general anesthesia group compared with 1 of 28 in the awake or moderate sedation (BIS 71–90) group. Airway issues occurred in 7 of 41 patients in the deep sedation or general anesthesia group compared with 0 of 28 in the awake or moderate sedation group.

Although the BIS monitor has seen the greatest use within and outside of the operating room, there are other monitors which may be useful in the arena of procedural sedation. One of the newer depths of sedation technologies that has been recently introduced into the operating room setting is entropy-based monitoring. Variability and irregularity in the processed EEG signals and electromyography (EMG) signals from the forehead are used to gauge depth of sedation based on CNS response to anesthetic agents. When compared to the BIS monitor, the entropy is different in that it uses not only the processed EEG, but also the EMG. This may allow not only a judgment of the depth of sedation, but also a measure of pain or the nociceptive input to the patient. In the normal, non-sedated state, there are high levels of entropy activity with considerable variability in both EEG and EMG signals. With an increasing depth of sedation, EEG cortical electrical activity becomes more regular with decreased variability. Likewise, the EMG forehead muscle activity decreases and ultimately ceases (low levels of entropy activity). To date, this technology has not been studied outside of the operating room.[81]

PREPARATION TO DEAL WITH AIRWAY AND CARDIORESPIRATORY ISSUES

Regardless of the agents used, route administered or the patient population, adverse airway, hemodynamic or respiratory effects may occur during procedural sedation. The first step in the prevention of such problems may be appropriately identifying the "at risk" population. To accomplish this task, most centers have adopted the policy that patients undergoing procedural sedation have the same evaluation as someone undergoing general anesthesia. The issues regarding this evaluation have been reviewed by the organization groups from pediatrics, anesthesiology,

and emergency medicine in the preparation of their aforementioned procedural sedation guidelines.

The pre-sedation assessment evaluates the patient's medical suitability for the proposed sedation. This determination is accomplished through the performance of a focused history and physical examination which includes the identification of any acute illness that may increase the likelihood of sedation-related complications. Further inquiry involves the identification of co-morbidities that may either mandate the use of special interventions or place the patient at a sufficiently high risk of morbidity that sedation is inappropriate. Since the primary risks associated with sedation include adverse respiratory or cardiovascular events, co-morbid features of these systems are the primary focus of this review. Additionally, given the potential for an increased incidence of adverse effects in such patients, the pre-sedation evaluation should focus on historical features that may be indicative of obstructive sleep apnea such as snoring or respiratory pauses during sleep and excessive daytime somnolence.

On physical examination, an upper airway assessment should be performed. The head and neck examination is used to identify the patient in whom endotracheal intubation or bag-valve-mask ventilation may be difficult or impossible to perform. Examples of this include those with a short neck, limited neck mobility, micrognathia, macroglossia, or limited mouth opening. A more objective measure of the airway commonly used by anesthesiologists is the Mallampati Scoring System. If the patient is Mallampati Grade III or IV (tonsillar pillars and uvula cannot be visualized), endotracheal intubation or effective bag-valve-mask ventilation may be impossible. While the possibility of a difficult airway does not preclude the use of procedural sedation, anesthesiology consultation or backup may be considered prior to the sedation.

During the pre-sedation assessment, it is also important to review the patient's previous experiences with procedural sedation. This is helpful in identifying both their effectiveness as well as the patient's perceptions of the experiences. Knowledge of previous bad experiences will help the practitioner in the selection of the specific sedative/analgesic agent as well as provide the opportunity to address specific patient concerns prior to entry into the procedure room. An additional component of the pre-sedation assessment is the establishment of when the patient last had any oral intake, to decrease the possibility of aspiration if airway protective reflexes are lost. The American Society of Anesthesiologists recommends that patients be NPO for 2 hours for clear liquids, for 4 hours for breast milk, and for 6 hours for solids or non-human milk prior to undergoing sedation for elective procedures.

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, it may be prudent to adhere, as much as possible, to the ASA guidelines. In patients undergoing semi-emergent or emergent procedures, who have not met the appropriate fasting guidelines, the use of H_2-antagonists and/or motility agents such as metoclopramide to decrease the volume and acidity of stomach contents may be considered. Alternatively, the safest option in select patients may be the induction of general anesthesia with endotracheal intubation to facilitate completion of the procedure and protect against aspiration.

Upon completion of the pre-sedation evaluation, the cumulative information gathered should allow the practitioner to determine the depth of sedation that will likely be required to effectively complete the procedure and allow them to make an informed decision regarding the agents to be used. If during the pre-sedation assessment it has been deemed unsafe to perform the sedation, the patient should be referred to a pediatric anesthesiologist for further evaluation.

TREATMENT OF AIRWAY OR RESPIRATORY PROBLEMS DURING SEDATION

Should airway, hemodynamic or respiratory events occur during sedation, prompt identification and intervention is generally effective in reversing these adverse events before permanent sequelae can occur. The first step in this process occurs before the procedure starts, with the assurance that the appropriate equipment is available for resuscitation should such problems occur. The resuscitation equipment and medications 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. Prior to the administration of any sedative agent, some of this equipment should be set out within arms reach or set-up including an appropriately sized bag-valve-mask device, Yankauer suction system, and monitoring devices. In most cases, an intravenous cannula is placed for the administration of sedative agents and resuscitation medications when needed. When sedation is provided by the administration of oral medications, the placement of an intravenous catheter is optional and can

be placed after the administration of the oral sedative and topical anesthetic cream. However, when deep sedation is planned, even if administered via the inhalation or oral routes, a functioning intravenous catheter should be placed in most cases. A frequently sited exception to this rule is the administration of IM ketamine (see above).

The primary response to airway and hemodynamic complications should be guided by general resuscitation guidelines such as those provided by pediatric advanced life support (PALS) or advanced cardiac life support (ACLS). Appropriate management of the ABCs (airway, breathing and circulation) is the priority. Treatment begins with the administration of supplemental oxygen if hypoxemia develops. A progressive management approach may then include repositioning of the airway or placement of a nasal airway to relieve upper airway obstruction, the application of continuous positive airway pressure (CPAP) to relieve laryngospasm, or bag-valve-mask ventilation for apnea. Following these resuscitation maneuvers, if an ongoing sedation infusion is being used, the infusion should be discontinued if the patient is still showing signs of possible airway or respiratory compromise. As needed, additional help should be summoned to aid in the resuscitation.

Frequently, airway, hemodynamic or respiratory events are short-lived following the administration of a bolus dose of a medication and resolve spontaneously once the plasma concentration dissipates. Rarely, endotracheal intubation and controlled ventilation are needed. Given the possibility that such care may be needed, personnel skilled in such procedures should be readily available. Those providing sedation should be trained in the basics of advanced life support techniques including bag-valve-mask ventilation. In some instances, reversal of opioids with naloxone or benzodiazepines with flumazenil may be indicated.

Naloxone (Narcan®) and its longer acting analogue, nalmefene, are pure μ-receptor antagonists and therefore can be used to reverse both the analgesic/sedative effects and side effects of opioids acting at the μ receptor. Naloxone is rapidly distributed, metabolized by glucuronide conjugation, and excreted in the urine, with a half-life of approximately 1 h in children and adults and 90 minutes to 3 h in neonates. The long half-life of some opioids compared to the short half-life of naloxone may require repeated doses or an infusion to avoid renarcotization. In addition to its shorter half-life, naloxone has lower affinity for μ receptors than most opioids, therefore it leaves the site of action more rapidly than even the shorter half-life would predict.

Nalmefene (Revex®, Ivax Corporation, Miami, FL, USA) is a naltrexone derivative that is a pure opioid antagonist without agonist effects. It has a longer duration of effect than naloxone and is a more potent antagonist than naloxone at all three main types of opioid receptors. Nalmefene is four times as potent as naloxone in antagonizing effects at the μ receptor and more potent than naloxone in antagonizing effects at the κ receptor. It is commonly stated that opioid antagonists such as naloxone and nalmefene have essentially no pharmacologic or physiologic effects in patients who have no opioids in their system. Doses as high as 4 mg/kg have been administered intravenously to healthy adult volunteers, without adverse physiologic effects. However, reversal of opioid sedation/respiratory depression with these drugs has been associated with significant complications including pulmonary edema, tachycardia, hypertension, and even death. Although these adverse effects are particularly prominent in children and young adults in whom pain is still present, they are unlikely to occur in the procedural sedation arena when these agents are used to reverse the acute effects of opioid administration. In addition to hemodynamic changes, seizures have been reported after naloxone administration, but only in patients with CNS pathology, receiving relatively large doses.

Some pediatric studies have employed routine reversal of opioid effect at the end of the procedure for which sedation/analgesia is administered. Previous reports of life-threatening complications after opioid reversal would dictate caution in advocating "universal reversal". Reversal should be employed only in situations in which respiratory depression/obstruction cannot be relieved with stimulation and airway positioning. Even in such situations, naloxone or nalmefene administration should be titrated in small increments to mitigate the respiratory depression and/or sedation without reversing analgesia. Although the dose of naloxone in children is recommended to be as high as 0.1 mg/kg with a maximum of 2 mg per dose, these doses are meant for patients presenting with acute opioid ingestions or intoxications. In the sedation situation, doses as low as 1–2 μg/kg should be used to achieve reversal of side effects only. For this purpose, the standard naloxone vial which contains 0.4 mg/mL (400 μg/mL) can be double diluted. One milliliter is diluted to 10 mL and then 1 mL of the resultant solution is diluted to 10 mL, resulting in a solution with a concentration of 4 μg/mL. Repeat doses can be incrementally administered at 2–3 minute intervals until there is reversal of respiratory depression.

Flumazenil is the only benzodiazepine antagonist currently available for clinical use. It competitively binds to central benzodiazepine receptors, thereby inhibiting GABA receptor activation. Whereas naloxone and nalmefene reverse both sedation and respiratory depression, flumazenil primarily reverses sedation with less effect on

respiratory depression. Flumazenil is only recommended for intravenous administration in the treatment of acute benzodiazepine intoxication; however, anecdotal experience suggests that intranasal administration may also be feasible. Flumazenil is relatively lipophilic, resulting in a rapid onset of action (1–2 minutes). Similar to naloxone, the duration of activity (40–80 minutes) is shorter than that of most benzodiazepines, so there is a risk of resedation. The recommended dose is from 10–20 µg/kg every 1–2 minutes to a maximum of 1 mg. Adverse effects occur in approximately 5% of patients and 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 or are being treated with other medications which lower the seizure threshold (tricyclic antidepressants, methylxanthines, and cyclosporine). Flumazenil has been reported to precipitate ventricular dysrhythmias when administered concomitantly with cocaine, methylxanthines, monoamine oxidase inhibitors, chloral hydrate, and tricyclic antidepressants. 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/hypoxemia and the ability to intervene by establishing an airway and assisting ventilation.

SUMMARY

Effective sedation and analgesia during procedures not only provides humanitarian relief of suffering, but also frequently facilitates successful and timely completion of the procedure. Adverse effects on hemodynamic and/or respiratory function may occur whenever sedative and analgesic agents are administered. It is important to note that no agent is totally devoid of the potential for life-threatening effects on respiratory and hemodynamic function. The occurrence of such problems and their impact on physiologic function can be lessened by the appropriate pre-sedation evaluation of patients, the monitoring of physiologic functions during sedation, and early intervention should problems arise.

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