Sedation in Children: Current Concepts

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Sedation in children poses a great challenge, with the main concern one of safety. The importance of providing adequate sedation to children was realized only in the last decade and a half, and relevant data are severely lacking. Use of potent sedative agents is not without risk. Children are given sedative agents in a wide variety of settings by practitioners with different degrees of experience with the drugs and management of adverse effects. Controversial issues must be addressed in this area, and appropriate tools developed to measure sedation and individualize treatment based on the drugs' pharmacokinetic and pharmacodynamic properties.
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OUTLINE

Children undergoing medical care are confronted with unfamiliar environments that may be perceived as potentially threatening. To soothe their fears and anxieties, several approaches are available, such as behavioral management, psychology, and pharmacology. A multidimensional approach is optimal; however, caregivers frequently resort to drug therapy because of inadequate time or resources.

The literature on sedation in children is somewhat limited, and clinicians make considerable extrapolation from adult literature. However, not only does the pharmacology of sedative agents differ in children compared with adults, but the time course of sedation differs. Adults usually require most pharmacologic intervention at the beginning of an illness, whereas children tend to need less at the beginning and more as they recover.

For any medical therapy, it is necessary to have an instrument that can detect problems and document treatment effectiveness. For sedation, developing such a tool is difficult since objective data are not easily obtained. A number of scoring systems discriminate different levels of sedation, but they have been slow to be accepted. The Vancouver Sedative Recovery Scale, which is validated for the pediatric intensive care unit (PICU) and postanesthesia recovery unit, rates 12 items in 3 categories—responsiveness, eye opening and function, and movements. The score is between zero and 22, with higher numbers given to more awake patients.[1]

The Neurobehavioral Assessment Scale (NAS) rated behavioral function in adults (age 18–72 yrs) undergoing maxillofacial procedures and was better than the Glasgow Coma Scale in differentiating levels of sedation.[2] The NAS rates

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four areas: sedation and reduced alertness, disorientation, speech articulation defect, and psychomotor retardation. The first three provided 97% of variance in scores; the contribution of psychomotor retardation may be small and its evaluation unnecessary. A more objective device that does not require observed behavior analyzes the neural network to classify electroencephalographic patterns against the depth of midazolam sedation during long-term sedation in the intensive care unit (ICU).[3] Even though it successfully classified level of sedation in only 50–60% of patients, the authors concluded that the scale compared with visual classification alone. However, it is limited in that it requires special equipment and expertise, and is not easily performed at the bedside.

We developed a sedation scoring system for our PICU (Figure 1). It has not been formally validated, but in practice it proved useful. A practical problem with validating tools such as those intended for the ICU is concomitant administration of analgesic agents that act as confounders and prevent a true evaluation of the efficacy of the sedative agent. Classic, validated analgesic scales have little or no application to assessment of sedation, although many have tried to use them for this purpose. When conscious sedation is necessary for procedures such as echocardiography and computed tomographic (CT) scans, a simpler tool may be more appropriate. A modified version of this scale is currently being used at one author's institution to monitor sedation for short procedures.

Thus, although many scoring systems are available to measure depth of sedation, an ideal does not exist. Development of such an ideal system is hampered by many factors, including difficulty eliminating subjectivity from assessment and the complex condition of patients in whom such scales might be most useful.

Pharmacologic Options

Pharmacologic sedation should not be a substitute for analgesics when a child is in pain, or for honest explanations about medical maneuvers and attempts at behavior modification. Distraction, relaxation techniques, and positive imagery can avoid sedation for many nonpainful procedures in which cooperation is necessary. These techniques achieved good cooperation in children as young as 7 years undergoing right heart catheterization for biopsies.[4] Using an age-appropriate video tape as an alternative to sedative agents, 92% of children (mean age 18.6 mo) successfully underwent cardiac ultrasound without sedation.[5] Certainly, when nonpharmacologic modalities fail, sedatives are appropriate.

General guidelines for sedation such as those set forth by the American Academy of Pediatrics should be adhered to when the drugs are delivered by a nonanesthesiologist.[6] These guidelines were developed due to increased use of sedatives during invasive diagnostic, radiologic, and minor surgical procedures performed in children outside the operating room. They were issued with the understanding that regardless of the intended level of sedation or route of administration, sedation represents a continuum from a loss of protective reflexes, through a light level of sedation, to obtundation.

The guidelines clearly define the extent of physiologic monitoring during various degrees of sedation, defined as follows:

1. Conscious sedation, a medically controlled state of depressed consciousness that allows the patient's protective reflexes to be

0	1	2	3	4	5		a	b	c
Coma	**Asleep**	**Drowsy**	**Calm**	**Awake**	**Wild**	HR	≤10%	Baseline	≥10%
Eyes closed	Eyes closed	Eyes open	Eyes open.	Alert	Anxious	BP	≤10%	Baseline	≥10%
No motion	Rare spon. motion	Moves < 0-5 times/min.	Moves <5-18 times/min.	Active, moves >10 times/ min.	Excess motion.	Resp.	≤10%	Baseline	≥10%
						Pupil	small	midsize	large
No head motion	No head motion.	No head motion. Moves	Minimal head motion.	Slow head motion.	Tosses head from side to				
No arm or leg motion. No reaction to stimulus	Minimal arm or leg motion. No reaction to mild stimulus.	arms or legs. Eyes open with mild stimulus.	Moves arms or legs. Moves on command.	Moves arms and legs. Easy to control movements.	side. Thrashes arms and legs. No control of movements.				

Figure 1. West Virginia University PICU sedation scoring system.

maintained, maintains a patent airway independently and continuously, and permits appropriate responses by the patient to physical stimulation or verbal command

2. Deep sedation, a medically controlled state of consciousness or unconsciousness from which the patient may not be easily aroused; it may be accompanied by partial or complete loss of protective reflexes, including inability to maintain a patent airway independently and respond purposefully to physical stimulation or verbal command
3. General anesthesia, a medically controlled state of unconsciousness accompanied by loss of protective reflexes, including inability to maintain a patent airway independently and respond purposefully to physical stimulation or verbal command.

Recommended physiologic monitoring for conscious sedation covers baseline vital signs, pulse oximetry or equivalent continuously during the procedure, intermittent respirations and blood pressure, continuous heart rate, and airway patency. After the procedure, the child should be observed in a well-equipped facility (presence of oxygen, bag mask, etc.) with frequent vital sign testing. Pulse oximetry and continuous heart rate monitoring should continue until the patient is fully alert. Deep sedation requires more stringent attention, including continuous cardiorespiratory monitoring with or without mechanical ventilation, and frequent blood gas monitoring depending on the patient's condition. This type of sedation is often necessary in the ICU.

For patients undergoing general anesthesia, anesthesiologists have minimal monitoring standards to which they adhere. Regardless of the situation, whenever sedation is required, the individual administering and monitoring the agent should be different from one performing the procedure.[7]

Chloral Hydrate

Experience with chloral hydrate as a sedative is extensive. Doses vary from 40–120 mg/kg orally or rectally, with the maximum single dose 2 g.[1] It is generally given to sedate children to allow completion of a diagnostic procedure. Thus, in most studies, if children achieved a motionless state sufficient to allow completion of a procedure after receiving a given dose of chloral hydrate, the agent was deemed to be a success. In a series of 295 patients undergoing CT examinations, 7% experienced side effects, with vomiting being the most common (4.3%).[8] The frequencies of hyperactivity and respiratory symptoms were less than 2%.

The success rate for sedation is usually around 86% for healthy children, whereas in those with neurologic disorders it tends to be lower.[9] In this study of 50 children, 43 were successfully sedated with a mean chloral hydrate dose of 58 mg/kg (range 25–81mg/kg). Seven patients who did not respond to the initial dose had neurologic abnormalities including intraventricular hemorrhage, cerebral palsy, brain tumors, and seizure disorder. Failure to respond ranged from being awake during procedures to requiring additional doses of chloral hydrate or a different agent (unspecified) intramuscularly and rescheduling procedures.

Because chloral hydrate does not increase intraocular pressure, it was recommended in children with normal or glaucomatous eyes who require ocular pressure measurements.[10] The suggested dose is 100 mg/kg for the first 10 kg body weight, and 50 mg/kg for each additional kilogram not to exceed 3 g in uncooperative children. In our experience this dose is excessive for most infants and some children. We recommend a starting dose of 50 mg/kg with incremental doses of 25 mg/kg up to 100mg/kg, not to exceed 1 g in infants and 2 g in older children. A different agent may be added if response to the maximum dose of chloral hydrate is inadequate.[11] Patients should be monitored closely after the procedure because delayed respiratory depression can occur with high doses of chloral hydrate. Respiratory depression also was observed after repeated doses for prolonged sedation.[12]

Chloral hydrate is perceived as a benign drug by many health care professionals, however, it can cause adverse effects at normal doses. A significant effect on diastolic blood pressure and expired carbon dioxide (CO_2; $p<0.02$ and <0.005, respectively) occurred in 26 healthy children (age 21–42 mo) who received doses of 25–75 mg/kg.[13] Both values were influenced by the dose and were elevated slightly with the highest dose. This result must be interpreted with caution, since children receiving higher dose were sleeping and the entire CO_2 was routed through the nostrils (and therefore diluted by dead space, resulting in lower concentration recorded from the nostrils); in children who received the lower dose and were crying, some CO_2 was expired from the mouth. Dental procedures also tend to

have an effect on cardiovascular function (due to crying, aggressive struggling, etc.), and this must be kept in mind when interpreting the results of this study.

Finally, a carcinogenic potential is associated with accumulation of trichloroethylene, a metabolite of chloral hydrate. The risk is theoretical, and evidence is insufficient to warrant selection of an alternative agent. Adverse effects that could result from repeated administration of chloral hydrate include central nervous system disturbances, decreased albumin binding, and metabolic acidosis, and predispose newborn infants to hyperbilirubinemia. In addition, data are insufficient to establish superiority of one sedative over another with respect to safety and efficacy. In 1993 the American Academy of Pediatrics Committee on Drugs issued a statement concluding that the drug is an effective sedative with a low frequency of toxicity when administered in recommended doses in the short term.[11] According to the committee, "A sudden switch by physicians and dentists from a sedative with which they are familiar to one with which they have less experience and for which there are not enough pharmacologic and safety studies in children may pose a greater immediate risk to children than a theoretical risk of carcinogenesis from short-term sedation with chloral hydrate." Additional well-designed studies are necessary to establish safety and efficacy of chloral hydrate in children.

Propofol

Propofol is one of the newest agents available for sedation in children. The ability to go from light sedation to general anesthesia and back to light sedation in a short time makes it an attractive agent for intravenous sedation. Propofol is an oil-soluble drug produced as a soy-based emulsion. The constitution and the caloric content of the emulsion are equivalent to the commercial fat emulsion preparation, Intralipid 10%, given as part of total parenteral nutrition. As such, the product is prone to bacterial contamination.[14] The manufacturer's recommendations are to change the entire propofol administration set every 6 hours when ampules are used for procedures and every 12 hours when glass bottles are used for continuous infusion.[15] This practice is time consuming and costly. Because of limited experience and the potential for general anesthesia, the manufacturer recommends that propofol be administered under the direction of an anesthesiologist. Despite this precaution, the drug is being given with increasing frequency by, among others, specialists in dentistry, radiology, cardiology, and ICU personnel.

For dental procedures (e.g., molar extractions) in handicapped patients, propofol has replaced nitrous oxide. Initially it was given as an intravenous infusion of 3 mg/kg/hour and gradually increased to 3.6 ± 0.65 mg/kg/hour during the procedures; this regimen provided satisfactory sedation in 90% of patients.[16] Another trial compared sedation with midazolam and propofol in 18 mentally or physically handicapped patients age 5–26 years who required restorative dental treatment or tooth extractions.[17] Induction and recovery times were much shorter with propofol than with midazolam, and the quality of sedation was considered better in the propofol group. Propofol was also preferred by patients and their parents since recovery was smoother and faster.

Before magnetic resonance imaging (MRI) studies, 30 children 1–10 years of age received induction anesthesia with halothane and nitrous oxide followed by a propofol loading dose of 2 mg/kg.[18] General anesthesia was then discontinued and propofol started at an infusion rate of 3, 4.5, or 6 mg/kg/hour during imaging that lasted for 55 ± 26 minutes. Induction and recovery times in the three groups were not significantly different. No child receiving the highest dosage moved during MRI, whereas 30–50% of children in the two lower-dosage groups did. No side effects such as nausea, vomiting, or significant cardiovascular instability occurred in any group. The authors recommend 6 mg/kg/hour during MRI to achieve maximum sedation and good compliance.

Data on continuous sedation with propofol in the PICU are limited.[19–21] The drug's pharmacokinetics and pharmacodynamics were studied in 28 PICU patients (age 0.13–182 mo).[22] After a loading dose of 2.5 mg/kg, infusion rates of 2–15 mg/kg/hour to achieve and maintain COMFORT scores[23] in the desired range of 17–26. Plasma concentrations at the end of the infusion ranged from 0.26–2.6 mg/L, a 10-fold variation. Most patients achieved concentrations of less than 1 mg/L with this regimen. Large interpatient variability was observed in pharmacokinetics, and no relationship between plasma concentrations and effect could be established. The drug was generally well tolerated with the exception of one patient who experienced hypotension possibly

due to propofol.

In our PICU, intravenous boluses of propofol 0.25 mg/kg are given until an appropriate level of sedation is attained. This loading dose is followed by a continuous infusion of 3 mg/kg/hour and titrated upward as necessary. A sedation algorithm may be used to adjust infusion rates (Figure 2). The algorithm shown in Figure 2 is used at our institution and is based on a sedation scoring system that was developed in-house. In general, the cost of treatment with propofol and the development of tolerance to the agent limit its use to less than 10 days for continuous sedation, although it has been given for up to a month without adverse effects to some patients.[24]

Propofol is associated with many complications, including opisthotonus, anaphylaxis (mostly bronchospasm and allergic edema), delayed recovery, resedation, bradycardia, and seizures.[25, 26] A 22-year-old woman was started on a continuous infusion of 50 µg/kg/minute and continued to receive the agent for 13 days without hemodynamic, pulmonary, or hematologic complications.[27] The dosage of propofol during this time was increased to 200 µg/kg/minute, giving the patient a huge caloric load and substantially increasing her partial pressure of CO_2. The infusion was discontinued, and 6 days later the patient had a tonic-clonic seizure that required benzodiazepines and a high-dose barbiturate to control it.

Five children (age 1 mo–6 yrs) with upper respiratory problems requiring intubation received propofol for sedation, after which they developed fatal metabolic acidosis and lipemic serum.[28] The authors speculated that the drug may have contributed to the deaths. Two large studies of sedation in pediatric patients found no association between death and propofol.[29] In late 1992, after reviewing reported cases of propofol-associated deaths worldwide, the Food and Drug Administration Anesthetic and Life Support Drug Advisory Committee concluded that no direct link could be established.[30]

Thus, it appears that the drug should be limited to short-term sedation for procedures. Until more experience is gained in the PICU setting, it should be administered only if all else fails or if the sedation is expected to be of short term, generally 24 hours or less. Deep or long-term sedation with this agent should be managed by an anesthesiologist.

Benzodiazepines

The availability of newer short-acting benzodiazepines and a specific antagonist, flumazenil, make this class of agents particularly attractive for sedation. Despite widespread application, the literature on some of the older agents such as lorazepam and diazepam for sedation in children is scant, although the drugs have been evaluated extensively as premedication due to their anxiolytic properties and as antiseizure agents.

Midazolam

Experience with the short-acting benzodiazepine

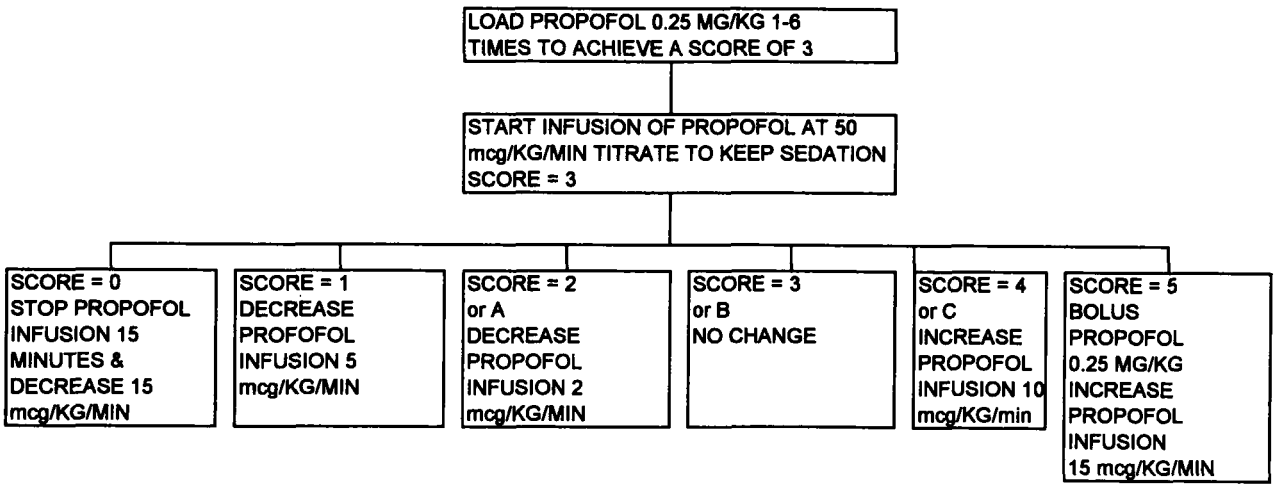

Figure 2. Algorithm for adjusting propofol infusion rates, based on the West Virginia University PICU sedation scoring system.

midazolam is rapidly growing in the United States. Although it is available only in an injectable form, it is administered by several routes. Given intravenously, midazolam 0.5 mg/kg was followed by 0.25 mg/kg at 2-minute intervals until sedation was achieved, with a maximum dose of 1 mg/kg. Doses as high as 0.6 mg/kg were completely effective in 47.5% of 57 children (age 4 mo–10.25 yrs) and partly effective (i.e., child struggled but procedure was completed successfully) in 38.5% for short procedures such as bone marrow aspiration, lumbar puncture, thoracentesis, and renal biopsy, as well as nonpainful procedures such as intubation and intravenous pyelogram.[31] The investigators reported lack of sedation in 14% of children. When effective, onset time was 4.3 minutes with a mean duration of 88 minutes. No hypoventilation occurred. Since the drug has no analgesic properties, meperidine up to 1 mg/kg was added for painful procedures. As would be anticipated, addition of the narcotic decreased blood pressure; the mean fall of 6 mm Hg was not dose related.

The results of this study seem somewhat paradoxic, since even in normal doses of 0.1 mg/kg midazolam can cause hypoventilation in susceptible patients. The cause for low effectiveness at seemingly high doses is not clear from the report. It seems prudent to avoid such high doses and administer combination therapy, rather than continue increasing doses of a single agent to unsafe levels if lower doses are ineffective.

Although an oral preparation of midazolam is not available, the injectable form is often given orally. The bitter taste may be masked by combining it with flavored liquids or adding it to flavored gelatin.[32, 33] Doses of 0.1–1 mg/kg have been given orally, but 0.5 mg/kg appears to be most effective, with minimal adverse effects. The onset of effect after oral administration is about 10–30 minutes, and the failure rate is 20%.[34]

Thirty children (age 1–6 yrs) scheduled for outpatient surgery were separated from their parents 10, 20, or 30 minutes after oral administration of midazolam 0.5 mg/kg.[35] Sedation and anxiolysis were assessed by two blinded observers at baseline, at the time of separation from parents, and at the time of induction of anesthesia. No difference in extent of anxiolysis was seen 10, 20, or 30 minutes after drug administration.

The intranasal route of midazolam administration is popular, although the failure rate is about 20%.[36] This route is often chosen because of its rapid onset and lack of need for patient cooperation. A limitation is that when large drug volumes are needed, the drug is not absorbed by the nasal mucosa but is delivered to the posterior pharynx where it is swallowed. Burning in the nose and eyes and occasional epistaxis make this route less popular for repeat administration. The recommended intranasal dose is 0.2–0.4 mg/kg.

Midazolam 0.3 mg/kg administered rectally is also effective, with onset of sedative effect generally within 20–30 minutes after administration.[37, 38] To administer midazolam rectally, the parenteral preparation was appropriately diluted and drawn up into a 10-ml syringe.[38] The syringe was connected to a gel-lubricated 3.5-mm outside diameter pediatric feeding tube, and the tube inserted about 3–4 cm into the rectum. After administration, the tube was flushed with 2 ml of air.

In the ICU, midazolam is administered by continuous infusion much as originally described.[39] Infusion rates of 0.4–4 μg/kg/minute after a bolus of 0.25 mg/kg appear to be a safe and effective (Figure 3).[39, 40] Combining midazolam with other drugs with sedative properties enhances the effectiveness of midazolam. After cardiothoracic surgery, 24 critically ill children were adequately sedated with midazolam 0.8–6.6 μg/kg/minute plus fentanyl 0.008–0.4 μg/kg/minute for analgesia.[41] This combination for sedation is not without complications. Respiratory arrest was reported after relatively normal dosages of the two agents administered together.[42]

Emergence delirium occurred in a 26-month-old child who received midazolam 0.5 mg/kg orally in grape juice before repair of a laceration.[43] Approximately 20 minutes after the dose, the laceration was sutured, and the child was observed for a further 40 minutes and discharged without complications. Approximately 1.5 hours after receiving midazolam (30 min after discharge), the child became extremely agitated and was brought to the emergency department. The signs of delirium included shrieking, hypervigilance, and fright. After 45 minutes of supportive care and observation, the child returned to her normal status and was discharged.

Midazolam is a short-acting agent and it is popular for conscious sedation. However, one should be aware of such paradoxic responses, and observation should probably continue for at

least 1–2 hours after a dose since peak concentrations in plasma after an oral dose occur at about that time.

Lorazepam

Lorazepam is useful for long-term sedation in the ICU. Due to its long half-life in neonates and infants it can be administered as a bolus dose every 6–8 hours.[44] According to practice guidelines for intravenous sedation and analgesia published by the Society of Critical Care Medicine, lorazepam is preferred for prolonged treatment of anxiety in critically ill patients.[45] Despite its abundant use in children, minimal data are available on its pharmacodynamics and pharmacokinetics during long-term sedation.

After a single low dose of lorazepam 0.03 mg/kg in 16 children (age 2.8–16 yrs), the trend was toward decreased anxiety by 24 hours, with some antegrade amnestic effect.[44] The terminal half-life of lorazepam was reported at 10.5 ± 2.9 hours. Continuous infusions for long-term sedation in the ICU was reported.[46] However, there is very little information on appropriate dosage, correct infusion concentrations, and compatibility with other intravenously administered drugs. The last is important for children, in whom intravenous access is often at a premium, making coinfusion of drugs necessary.

A randomized comparison of lorazepm and midazolam in adults reported that lorazepam was superior for time to return to baseline mental status.[46] This could potentially shorten the ICU stay and reduce costs. The authors also suggested that dosages of benzodiazepines required for sedation may be higher than currently recommended in the literature. Another author also found that continuous infusions of lorazepam were cheaper and more cost effective than midazolam by that route[47]; however, that report was based on data collected during the course of the author's day-to-day practice and did not stem from a controlled study, so the results should be interpreted with caution.

Finally, very large volumes of fluid may be required to deliver continuous sedation since lorazepam's compatibility with various intravenous fluids in concentrations greater than 0.16 mg/ml and its adherence to the polyvinyl and polyolefin bags are major problems.[48, 49] In children in whom intravenous access is difficult, continuous infusions may not be feasible due to lack of data

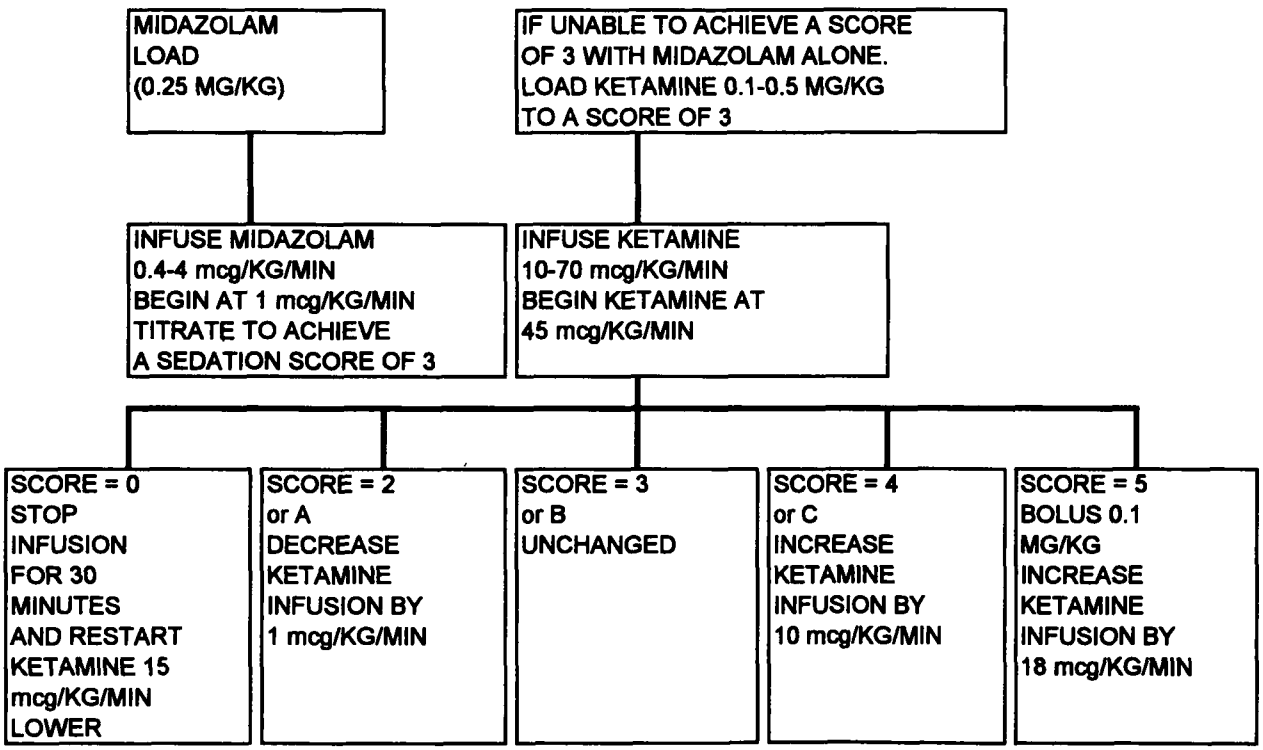

Figure 3. Algorithm for adjusting midazolam and ketamine infusion rates, based on the West Virginia University PICU sedation scoring system.

on compatibility of lorazepam with common intravenous fluids such as parenteral nutrient solutions.

Rhythmic, myoclonic jerks occurred as early as 1 minute after administration of lorazepam to premature infants.[50] The author hypothesized that alcoholic solvents in the injection formulation may be responsible for this neurotoxicity and recommended avoiding them whenever possible. Benzodiazepine solutions for oral administration prepared in propylene glycol and polyethylene glycol tend to cause diarrhea and should be avoided.[51]

Diazepam

Diazepam, although considered a prototype intravenous sedative agent, has not been a popular sedative agent since the introduction of the shorter acting agents such as midazolam. The Society of Critical Care Medicine no longer recommends it for critically ill ICU patients due to pain and thrombophlebitis that usually occur when administered peripherally; its long duration of action, which may potentially cause oversedation due to accumulation; and large fluid volumes that may be required in continuous infusion.[45] Its main indications remain the treatment of status epilepticus and for short procedures such as endoscopy and radiation therapy (see below).

Ketamine

Ketamine provides sedation with minimal respiratory and hemodynamic compromise, and has the advantage of inherent analgesic properties due to effects on the opioid and serotonergic systems. Its bronchodilatory properties make it an attractive drug when sedating patients with asthma. However, ketamine produces copious airway secretions and may also increase airway responsiveness with possible laryngospasm.[52,53]

An oral preparation is not available, but similar to midazolam, the drug may be administered orally by mixing the injection formulation with a beverage. However, failure rates as high as 35% have been reported with this route. Oral sedation is usually begun with 5 mg/kg for patients with normal mentation, although doses have ranged from 1–10 mg/kg.[34,54] Time to onset is about 20 minutes, similar to that of midazolam, but recovery time is slightly longer. The frequency of nausea and vomiting also is higher for ketamine than for midazolam.

In mentally handicapped patients, the required oral dose is increased and appears to correlate with level of impairment. In severely handicapped patients, a higher starting dose of 8 mg/kg attains adequate sedation, and doses as high as 36 mg/kg may be required in profoundly mentally handicapped patients.[55–57]

Like midazolam, ketamine is effective intranasally. A dose of 6 mg/kg is recommended. Time to onset is 20–40 minutes, with a success rate of 78%.[58] Rectally administered ketamine 5 mg/kg is also efficacious; time to onset is similar to that with other routes of administration.[38]

In a case series reported in 1989, ketamine 4 mg/kg intramuscularly was administered to children in an emergency department to facilitate various procedures.[59] In most children, adequate conditions for performing the procedures were reached within 5 minutes, and 86% of procedures were completed without additional local anesthetic agents. The only clinically significant complication was a single case of laryngospasm that did not require intubation.

Ketamine is often given for sedation in the cardiac catheterization laboratory. By keeping the incremental dose low (0.5–1 mg/kg intravenously), the frequency of respiratory compromise such as central apnea was reduced to 3% in 157 patients age 1 month–20 years.[60] The drug is particularly effective in this setting because it does not suppress aberrant cardiac conduction pathways, as do other sedative and analgesic agents such as morphine.

Alterations in hemodynamics associated with ketamine for sedation are said to be small.[61] This finding was challenged, however, as the drug was implicated in the production of pulmonary hypertension in a limited number of patients with baseline elevated pulmonary vascular resistance.[62] In these patients ketamine consistently increased oxygen consumption and raised pulmonary artery pressure.

In the PICU ketamine is administered by continuous intravenous infusion, especially in patients who have undergone cardiac surgery. Children undergoing cardiac surgery, and those requiring intubation for exacerbation of underlying pulmonary disease such as bronchopulmonary dysplasia, were given a continuous intravenous infusion of 10–15 and 16–32 μg/kg/minute, respectively.[63,64] At these dosages, some supplemental midazolam was required. One group also administered a 1-mg/kg starting dose.[63]

In the PICU at our institution, when ketamine infusion is given for continuous sedation the patient receives a loading dose of up to 0.5

mg/kg, followed by a continuous infusion of 10–70 μg/kg/minute, with upward titration depending on the sedation score (Figure 3). When given for long-term sedation (generally > 48–72 hrs), the infusion rate should be kept as low as possible to minimize the occurrence of myoclonic movements when the drug is removed. We observed myoclonic movements persisting for a month after cessation of therapy.

The psychomimetic side effects of ketamine, such as vivid dreams and confusion on emergence from sedation, are reduced by benzodiazepines such as midazolam. Hence the combination is desirable to minimize these psychic adverse effects, which are most obvious in adults but could occur in children as well.[64] Thus, although ketamine is an alternative for sedation in the PICU, it should be prescribed with extreme care, preferably under the guidance of an anesthesiologist, since it has a potential for serious adverse effects.

Barbiturates

Barbiturates have considerable sedative properties. Compared with many newer drugs, they have longer duration of action and narrower therapeutic indexes. Familiarity with barbiturates, several available routes of administration, and the ability to combine them with drugs from other classes make them a frequent choice. Pentobarbital, secobarbital, and methohexital are given for short-term conscious sedation for special procedures such as CT scans and radiation therapy.[65–70]

Pentobarbital 2.5–7.5 mg/kg intravenously successfully provided sedation in children before MRI scans.[66] Secobarbital provides effective sedation for newborns in the ICU. Because of its long duration of action and possibility of accumulation, prolonged sedation can occur, but it can be avoided by keeping the dosage below 7 mg/kg/day.[67]

Methohexital has a rapid onset and a fairly short duration of effect. An advantage in the pediatric setting is its effectiveness by several routes of administration, including intravenous, intramuscular, and rectal. The ability to give it intramuscularly makes it preferred over thiopental. In doses of 10 mg/kg intramuscularly, sedation for CT scans lasts for 35 minutes, with a failure rate of 33%. One group supplemented patients with ketamine 1–2 mg/kg if sedation with methohexital was inadequate.[68] Rectal methohexital 25 mg/kg was given before MRI with a success rate of 87%.[69] In this study, 190 children requiring sedation for MRI or CT scans were sedated with rectal methohexital (102 patients, mean age 25 ± 2 mo) or oral chloral hydrate (88, mean age 28 ± 3 mo). The drugs provided adequate sedation in 87% and 83% of patients, respectively. In many cases the duration of sedation with methohexital was shorter than the MRI, resulting in inadequate studies. Children sedated with chloral hydrate required a longer period of observation in the radiology department.

Intravenous methohexital is effective in children with cancer for painful procedures such as bone marrow biopsies and radiation therapy. In one study, incremental doses were 1 mg/kg, the mean total dose required for sedation was 5.6 mg/kg, and the duration of sedation was 30 minutes.[70] Clinically insignificant decreases in diastolic blood pressure and ventilation complications requiring bag mask and simple suctioning occurred in 17.4% and 1.5% of patients, respectively. Other minor complications requiring no intervention, such as transient behavioral changes, transient myoclonus, and minimal stridor, occurred in six patients.

Although barbiturates are effective and relatively safe sedative agents, it is essential to monitor hemodynamics and oxygenation, and have available emergency respiratory support equipment for intubation when they are administered.[70] The agents do not have any analgesic properties, so for painful procedures, analgesics should be added to the sedative regimen.

Narcotics

Narcotics are widely used for sedation; however, administration for prolonged periods in the absence of pain leads to physical dependence. Morphine is the prototype, but synthetic narcotics such as fentanyl and alfentanil are increasingly popular and are less sedating than the natural opioid compounds.

Alfentanil

Alfentanil is the shortest-acting of approved narcotics. It is effective for continuous sedation during cardiac catheterization in children after premedication with a benzodiazepine such as midazolam. During cardiac catheterization, 14 infants (age 1–17 mo) were sedated with alfentanil 24 ± 8 μg/kg initial bolus dose followed by 32 ± 8 μg/kg/hour infusion.[71] In cyanotic

versus acyanotic infants, mean ± SD dosages were 21 ± 6 versus 28 ± 8 μg/kg/hour. Cyanotic infants received the lower dosage as a precaution against further worsening of respiratory status, since all narcotics have a potential to suppress respiration.

Alfentanil with fentanyl were compared during cardiac catheterization in 13 patients age 1–23 months.[72] Initial bolus doses were 20 ± 6 and 2.5 ± 1.1 μg/kg, respectively, they were followed by intravenous infusions of 30 ± 12 and 1.5 ± 0.6 μg/kg/hour, respectively. Drug requirements were comparable for all patients regardless of age or oxygen saturation in blood. The frequency of nausea and vomiting after sedation as well as length of sedation were comparable for both agents.

Another study of patients undergoing a Fontan procedure compared alfentanil with fentanyl.[73] The loading dose was decreased to 4.4 ± 2.7 μg/kg and the intravenous infusion to 10.3 ± 8.6 μg/kg/hour. These doses were lower than those for surgical anesthesia and are explained by a lower degree of noxious stimulation associated with cardiac catheterization than with cardiac surgery. The regimen produced successful sedation in all 14 patients (age 5–20 yrs).

The potential for respiratory depression requires that patients receiving alfentanil be observed closely in the immediate postoperative period. For this reason, administration of the drug outside the operating room is not recommended.

Fentanyl

Fentanyl is given to provide sedation in ICUs as well as for special procedures. In one study, patients undergoing cardiac catheterization received an initial intravenous bolus dose of fentanyl 2.5 μg/kg followed by a continuous infusion at 1.50 μg/kg/hour. Concerns regarding airway safety may require the presence of an anesthesiologist for this type of sedation.[72] Fentanyl 0.68 ± 0.24 μg/kg/hour was given by continuous infusion for 86 ± 47 hours to neonates and preterm infants in the neonatal ICU to determine its sedative and analgesic effects.[74] Although it was effective and required fewer supplemental sedative doses as well as catecholamines, meconium was excreted later and higher bilirubin levels were reached earlier than in patients not receiving the agent. Heart rate and blood pressure were not significantly changed by fentanyl. The drug should be administered to neonates under strict indication, and the duration of therapy should be limited to as short a time as possible to avoid undesirable adverse effects, including tolerance.

For pediatric patients who do not have indwelling catheters, the preferred route of fentanyl administration is transmucosal. Oral transmucosal fentanyl citrate (OTFC) is available in a lollipop form and has bioavailability of approximately 50%. In 10 patients (age 6–34 yrs) in a study conducted in an emergency department, OTFC was administered in two doses, 10–15 μg/kg and 15–20 μg/kg, based on extent of patient discomfort, type of procedure (laceration repair, abscess drainage, etc.), and degree of pain associated with it.[75] Patients were asked to suck an appropriate lollipop as fast as they could. The average dose consumed was 13.7 ± 2.4 μg/kg. Patients required approximately 12 minutes to consume the dose. Sixty percent of patients became sedated in 12–30 minutes after starting OTFC consumption. No hemodynamic adverse effects were noted.

Plasma fentanyl concentrations peak in about 20–30 minutes, and in healthy volunteers bioavailability is 50%.[76] The most common side effects of OTFC are pruritus, dizziness, and dry mouth; nausea and vomiting have also been reported.[75]

Sufentanil

No studies have compared synthetic narcotics, but a major impact of this form of sedation is cost. Sufentanil is more expensive than alfentanil or fentanyl and is much more potent than fentanyl. Its use outside the operating room is extremely limited, although it may be given in the PICU. Like fentanyl and alfentanil, when sufentanil is administered outside the operating room, it should be under the strict supervision of an anesthesiologist. Due its high potency, it is useful in patients with fluid restriction who require high dosages of narcotics, since the drug's fluid volume is considerably less than that of fentanyl.

Sufentanil 0.013–0.017 μg/kg/minute was given by intravenous infusion and titrated down to 0.004–0.006 μg/kg/minute when it was time to wean patients from the ventilator.[77] Whereas no obvious complications occurred at any time during this study, including in the weaning period, the authors cautioned against administering the drug to hypovolemic patients in whom hypotension could occur at those dosages.

Volatile and Inhalational Agents

Isoflurane may be given for continuous sedation in the PICU, but hallucinations, generalized seizures, and disorientation may occur after its withdrawal and may last for up to 5 days.[78] Isoflurane was administered for sedation in the PICU at concentrations ranging from 0.1–0.6% in an air-oxygen mixture and compared with midazolam 0.02–0.2 mg/kg/hour in patients requiring sedation for more than 24 hours.[79] Sedation was rated on a 6-point scale. The agents were discontinued when patients were ready to come off the ventilator. Plasma isoflurane, midazolam, and 1-hydroxy midazolam concentrations did not correlate with sedation scores. No undesirable side effects were associated with either agent. The authors concluded that isoflurane is a suitable alternative for sedation of mechanically ventilated patients who require long-term (> 24 hrs) sedation.

A crossover study compared propofol and isoflurane in 24 medical and surgical patients requiring sedation.[80] No clinically significant differences between agents were seen in the quality of sedation or time to recovery from sedation. Two patients developed peripheral neuropathy. They were randomized to receive propofol for 24 hours followed by isoflurane for as long as sedation was necessary. They received isoflurane for 151 and 254 hours, respectively, compared with other patients in whom duration of therapy was 10–147 hours. The peripheral neuropathy resolved over 4–12 months in these patients. It does appear to be a problem with prolonged isoflurane administration.

Other problems associated with volatile agents are decreased sedation during airway treatments and trachea suctioning, and severe auditory and visual hallucinations, as occurred in three patients in this study.[80] Thus, it seems that isoflurane is a potent agent with many adverse effects associated with short- and long-term administration. It is recommended that it be given under the direct supervision of an anesthesiologist.

Nitrous oxide is different from other common volatile agents (halothane, isoflurane) in that it has analgesic properties. Nitrous oxide at a concentration of 35% was widely administered in dental studies to augment sedation and analgesia. Adding it to hydroxyzine preoperatively produced better sedation than either alone.[81] The major problem with volatile agents for sedation is adequate scavenging of waste gases.

Other Agents

α_2-Adrenergic Agonists

The α_2-adrenergic agonists such as clonidine have emerged as a group of sedative agents that cause no or minimal respiratory depression at therapeutic dosages. They also have analgesic properties because they prevent the release of substance P, a mediator of noçiceptive stimuli.

The dose of clonidine for sedation is 3–5 μg/kg. In normotensive children, this does not produce hypotension, although bradycardia was reported.[82] When drugs in this class are given in combination with other sedative agents, caution must be exercised because of potential for excessive sedation. This may be explained by alteration in distribution of the second drug being induced by the α_2-agonist.[83]

The literature on these agents is limited. As new information accumulates the drugs may emerge as effective for sedation.

Procedure-Directed Sedation

CT Scans and MRI

Sedation is required to keep patients motionless during imaging procedures that last for more than a few minutes. Patients undergoing MRI require deep sedation, since, compared with CT scans, the tunnel they are placed in is longer and more confining, and the procedure is noisy. The MRIs usually last for 30–60 minutes, and a typical CT scan lasts for 15–30 minutes.

According to a national survey of sedation practices during CT scans, chloral hydrate was the most commonly administered drug.[84] In a retrospective analysis of sedation for CT and MRI procedures in 1158 children age 1 day–18 years, in children younger than 18 months oral chloral hydrate 60–120 mg/kg was the most common agent.[85] For those older than 18 months, the drug of choice was intravenous pentobarbital 2–6 mg/kg. For 407 outpatients who underwent CT, the combined success rate for both regimens was 97%. Of 765 patients who underwent MRI, 725 achieved successful sedation, with a success rate of 96% for the regimens combined. In another study, rectal midazolam 0.3–0.6 mg/kg produced satisfactory sedation in only 58% of patients.[86]

In one comparison trial, methohexital 25 mg/kg was administered rectally after diluting the injection preparation to 10% solution with sterile water.[69] Doses were repeated every 15 minutes to

a maximum of 500 mg if the child was not sedated adequately with the initial dose. Chloral hydrate was administered orally as a single dose of 50–100 mg/kg and repeated as necessary to a maximum of 1000 mg. Sleep time was shorter with methohexital (46 vs 66 min), resulting in fewer successfully completed MRI scans (69%) compared with chloral hydrate (85%). The shorter half-life (2–4 hrs) of methohexital compared with chloral hydrate (10–12 hrs) meant that children could be discharged sooner. For CT scans, methohexital was superior to chloral hydrate (97% vs 77%).

Propofol is often chosen for MRI in patients who are difficult to sedate because of precise control over sedation that it provides. A comparative study evaluated pentobarbital given in incremental doses of 2.5 mg/kg until satisfactory sedation was achieved, with a maximum dose of 7.5 mg/kg, and propofol 2 mg/kg followed by supplemental doses of 1 mg/kg until sedation was satisfactory. The level of sedation was maintained with a continuous intravenous infusion of propofol 6 mg/kg/hour. Both drugs were effective, but the group receiving propofol had a higher frequency of oxygen desaturation and bradycardia than the pentobarbital group.[45] This reemphasizes the need for the presence of an anesthesiologist during propofol sedation.

Echocardiogram

Echocardiogram is a noninvasive procedure, but positioning the electrical probe on the chest and the pressure applied during imaging can cause discomfort and patient movement, which could affect the results. Thus, these patients are sedated. The room where echocardiograms are performed is usually dark, which augments sedation.

The efficacy of oral or rectal chloral hydrate and thiamylal was evaluated prospectively in 45 infants, children, and teenagers (age 1 day–19 yrs) who underwent cardiac catheterization and two-dimensional Doppler echocardiographic examination.[87] Oral or rectal chloral hydrate 50–70 mg/kg or thiamylal 22 mg/kg was necessary to provide sufficient sedation, and were equally efficacious. A problem with chloral hydrate is the lag time associated with onset of sedation.

Intranasal midazolam 0.2 mg/kg was given to 15 infants (age 4–36 mo) undergoing echocardiograph, with the dose repeated in 5–15 minutes as necessary.[88] All but one examination was completed successfully. In the one that failed, the second dose was lower than 0.2 mg/kg and given at 15 minutes, which was late for that patient. The authors recommended 0.2 mg/kg for both starting and repeat doses, and if a repeat dose is necessary (uncooperative or agitated child), it should be administered as early as 5 minutes after the initial one.

Intranasal midazolam is absorbed much faster and therefore its relative safety compared with oral midazolam may be much lower. Adverse effects such as apnea could occur easily with this route of administration. Although the literature contains reports of its administration by nonanesthesiologists, extreme caution should be exercised when it is given by individuals with little or no experience with the intranasal route.

Dental Procedures

Children may require sedation during dental procedures not only to reduce discomfort due to being confined in the chair, but because of pain and apprehension. Midazolam given rectally was more effective than when given orally to uncooperative children.[89] Studies found that, compared with oral administration, with rectal administration the procedure could be started sooner, the duration of sedation after procedure was shorter, and a lower dose was given.[89, 90]

In a study of 24 children (age 18–48 mo) the combination of chloral hydrate 50 mg/kg and promethazine 1 mg/kg orally was no more effective than meperidine 1 mg/kg and promethazine 1 mg/kg orally in providing sedation for dental procedures; 48–50% of patients in both regimens had a significant frequency of oxygen desaturation.[91, 92] Other side effects were nausea and vomiting. Chloral hydrate-promethazine had significantly better results for sleep ($p=0.001$) and overall behavior ($p=0.019$).

In a double-blind, crossover study of 20 children (age 20–60 mo) chloral hydrate 50 mg/kg plus hydroxyzine 25 mg/kg or temazepam 0.3 mg/kg (route of administration unspecified) produced similar sedation and no significant difference in frequency of desaturation or overall behavior.[93] In another dental study comparing chloral hydrate-promethazine with hydroxyzine-diazepam, the latter combination led to significantly better behavior ($p<0.05$) than the former.[94] Oral triazolam 0.02 mg/kg and chloral hydrate 40 mg/kg plus hydroxyzine 25 mg/kg

provided similar sedation.[95]

The chloral hydrate dose was increased to 50 mg/kg, the hydroxyzine pamoate dose remained 25 mg/kg, and meperidine 1.5 mg/kg was added to the regimen.[96] All drugs were administered orally. This combination led to better behavior than the protocol without meperidine and was associated with no increases in side effects. However, a similar study that gave chloral hydrate 40 mg/kg and meperidine 0.5 mg/kg, and maintained the hydroxyzine dose at 25 mg/kg showed no benefit to the addition of meperidine.[97] The results of these studies suggest that the combination of chloral hydrate 50 mg/kg, hydroxyzine 25 mg/kg, and meperidine 1.5 mg/kg would achieve optimal dental sedation.

Ketamine 6 mg/kg (injection preparation given orally) was compared with oral meperidine 2 mg/kg plus promethazine 0.5 mg/kg in 40 children (age 20–60 mo) undergoing a variety of outpatient dental procedures. Ketamine provided more rapid sedation than the combination regimen. The overall quality of sedation and time to recovery were marginally different between the groups; however, ketamine was associated with more vomiting.[98] When submucosal morphine 0.15 mg/kg was compared with oral meperidine 2.2 mg/kg, both administered with promethazine 1.1 mg/kg orally, to children (age 2–7 yrs) undergoing dental procedures, no differences were seen in overall effectiveness or sedation.[99]

Intensive sedation for extremely painful dental procedures may require general anesthesia. Midazolam and propofol were compared for such procedures in a double-blind, crossover study in handicapped patients.[17] A bolus dose of midazolam 0.02 mg/kg was followed by a continuous infusion of 6.6 µg/kg/minute. Propofol 0.2 mg/kg bolus was followed by 4 mg/kg/hour. Midazolam was inferior to propofol, since induction time was less predictable and recovery took longer.

In summary, morphine can be substituted for meperidine, and triazolam, diazepam, or midazolam for chloral hydrate to provide sedation for pediatric outpatient dental procedures. In mentally or physically retarded or combative patients who are very difficult to handle, oral ketamine in place of chloral hydrate appears to be advantageous. Pulse oximetry should be performed for any sedated patient requiring these agents. Adverse effects such as nausea and vomiting may be expected. Potent drugs such as ketamine, propofol, and midazolam should be handled only by experienced personnel.

Oncology Procedures

A number of comparative studies investigated sedative regimens that might be effective in this group of patients. In a comparison of midazolam and fentanyl for premedication before painful procedures in 25 patients, midazolam was preferred by most patients due to the amnesia it produced.[100]

Midazolam and propofol were assessed in 90 children and adults who required central venous access for chemotherapy or total parenteral nutrition.[101] Results were similar for midazolam 0.02 mg/kg initial intravenous bolus repeated every 2 minutes until a predefined level of sedation was achieved. This level of sedation was then maintained using 0.005-mg/kg increments. Propofol 0.75–1.0 mg/kg initial intravenous bolus was followed by 0.25-mg/kg bolus, or infusion of 2–4 mg/kg/hour to achieve the same predefined level of sedation during central line placement. Both drugs provided excellent sedation with minimal side effects. Midazolam produced the best amnesia and propofol (bolus and infusion) the fastest recovery. The time to reach the predefined level of sedation was significantly shorter with the propofol bolus than with midazolam and propofol infusion ($p<0.0001$). Propofol infusion led to faster recovery than the bolus despite the fact that higher dosages were necessary to achieve the sedation level in this group. The authors concluded that the optimal approach is midazolam bolus followed by propofol infusion.

Intensive Care Procedures

Seven sedative regimens for ICU analgesia and sedation were compared.[102] For ventilated patients fentanyl-midazolam and alfentanil-midazolam combinations were superior to ketamine, flunitrazepam, meperidine, promethazine, and meperidine-flunitrazepam. Sedation was similar with propofol and isoflurane.[80] Propofol was infused at a rate of 6–150 µg/kg/minute and the inhaled isoflurane concentrations ranged from 0.1–0.8%.

Sedation is often chosen in ICUs to achieve the optimum oxygen supply:demand ratio. In a comparison of sedation with propofol, midazolam, thiopentone, and fentanyl, propofol reduced oxygen uptake (VO_2) the most (15%), followed by midazolam (12%) and thiopentone

Table 1. Pediatric Withdrawal Scoring System

Signs and Symptoms	Score	Signs and Symptoms	Score
Crying		Sweating	1
Excessive	2	Fever	1
Continuous	3	100–101°F	1
Sleep after feeding		> 101°F	2
< 1 hr	3	White blood cells > 20,000	3
< 2 hrs	2	Mottling	1
< 3 hrs	1	Nasal stuffiness	1
Moro reflex		Respiratory rate	
Hyperactive	2	10% above normal	1
Markedly hyperactive	3	10% above normal + retractions	2
Tremors		Sneezing	1
Mildly disturbed	1	Nasal flaring	2
Moderate–severely disturbed	2	Excessive sucking	1
Mildly undisturbed	3	Poor feeding	2
Moderate–severely undisturbed	4	Regurgitation	2
Increased muscle tone	2	Projectile vomiting	3
Yawning	1	Stools	
Excoriation	1	Loose	2
Seizures	5	Watery	3
White blood cells > 20,000, no fever	4	Peripheral erythema	3

Scores above 8 are considered withdrawal.
From reference 107.

(10%).[103] Of interest, fentanyl raised VO_2 by 5%.

Endoscopy

Various doses of meperidine and diazepam in combination for endoscopy were compared in a randomized double-blind trial. Meperidine 2 mg/kg was superior to meperidine 1 mg/kg plus diazepam 0.1 mg/kg, meperidine 2 mg/kg plus diazepam 0.1 mg/kg, and diazepam 0.1 mg/kg alone.[104] Addition of the benzodiazepine increased the frequency of negative behaviors such as need for emotional support, verbal resistance, verbal fear, unintelligible verbalization, crying, and screaming in 9% of the 71 patients age 1–19 years.

Withdrawal of Sedative Agents

Although sedation is often necessary for successful interventions, ceasing sedation is often associated with difficulties. Withdrawal reactions are fairly common. Unfortunately, the literature on methods of weaning sedation is extremely limited.

All 23 children (age 1 wk–22 mo) who were sedated with fentanyl for a total dose of 2.5 mg/kg or for more than 9 days experienced withdrawal reaction.[105] The reaction may also occur in children who receive propofol infusion for 4 or more days in whom the drug is stopped abruptly. Withdrawal has been reported in two children age 15 months and 2 weeks, respectively, who received midazolam for 2–4 weeks.[106] Abrupt discontinuation of midazolam led to restlessness, tachycardia, hyperpyrexia, and aerophagia in one child. In both patients, midazolam was reinstituted and later substituted with clorazepate from which they were weaned successfully.

In children, withdrawal from sedation is often associated with aerophagia and distention of the stomach, leading to vomiting. In addition, it may precipitate fever and cardiac, respiratory, and neurologic effects. Careful weaning from long-term sedation is therefore important.[106] Withdrawal symptoms must be evaluated critically so that they may be treated quickly.

Decisions regarding the presence of withdrawal are hard to make. A scoring system was developed to evaluate signs and symptoms in children experiencing withdrawal reaction.[107] We modified it to include other findings we associate with withdrawal (Table 1). In a PICU, a score higher than 8 is considered to be withdrawal. Many scores are available for neonates born to addicted mothers; most are useful for older infants and children in the ICU when applied individually. However, comparative data evaluating their efficacy are lacking, making it hard to choose the right one.

Children who awake from sedation in a strange environment may have many disturbed reactions.

In addition, although they have been sedated, they have not necessarily had sleep, particularly rapid eye movement (REM) sleep, and some reactions thought to indicate withdrawal are characteristic of deprivation of REM sleep.[108] Many sedative drugs deplete the brain of central neurotransmitters. This imbalance results in inability to experience REM sleep and may also be responsible for producing some of the reactions seen on emergence from sedation. The emergence reaction resembles central anticholinergic syndrome and can be readily treated with physostigmine.

When it is clear that the patient is withdrawing, a weaning program should be instituted. Methadone is a good choice for narcotic withdrawal because it has a lower frequency of inappropriate opioid binding than morphine, and its long duration of action and good bioavailability make it effective.[109, 110] To determine the amount of narcotic needed per day, the 24-hour requirement for the intravenous opioid currently being given is calculated, and an equipotent dose of methadone is given intravenously in three to four divided doses. Orders should be written for breakthrough doses of intravenous methadone 0.05–0.1 mg/kg if the patient shows sign of withdrawal. After changing over to methadone, the patient should be stabilized for 24–48 hours with no symptoms of withdrawal before beginning to taper the dose. The 24-hour dose is then decreased by 10–20% every day. The rate of tapering may have to be slowed in small infants to dosage reductions of 10–20% per week. In the event that the child does exhibit withdrawal symptoms with a tapered dosage, the dosage before the taper should be resumed and the drug titrated down again at a slower rate. This regimen is used by several institutions including our own.[109, 110] A similar regimen may be adopted for orally administered opioids.[111]

Oral clonidine 3–5 μg/kg every 8 hours may also minimize withdrawal symptoms and allow faster weaning of the narcotic. Hypotension is rarely a problem, but bradycardia may occur and necessitates decreasing the dosage or discontinuing clonidine. If clonidine is given to facilitate weaning, it should be tapered over 5–7 days if the patient has been receiving it for more than 6 days.[112–116]

When continuous intravenous infusions of sedative are given for more than 48 hours, gradual tapering of the agent(s) is recommended. This is particularly true for propofol and midazolam. Weaning propofol at a rate of 10% every 2–3 hours usually keeps the patient from withdrawing.[117, 118] When midazolam is given for prolonged periods, lorazepam is often substituted because of its long duration of action and availability of an oral formulation. Usually lorazepam 0.02–0.05 mg/kg orally or intravenously every 8 hours together with additional doses of 0.05 mg/kg every 2 hours as necessary for breakthrough withdrawal symptoms will keep the child from withdrawing. Once stabilized, the dosage is slowly decreased by 20 % every 48 hours.[119]

Summary

The ideal sedative drug does not exist, and tolerance will develop over time with all the drugs discussed. An approach that focuses on the patient's specific needs, balancing sedation, analgesia, and amnesia requirements, provides the best results. This extensive evaluation of the literature suggests that there is no one right way of achieving sedation in children. Many roadblocks exist, including lack of validated scoring systems that can measure the degree of sedation with accuracy and difficulty identifying the presence of withdrawal. As long as subjectivity is associated with measuring sedation, the results of clinical studies will remain inconsistent and biased.

Until good scoring systems are developed, it seems wise to become familiar with and follow the practice guidelines developed by the Society for Critical Care Medicine. Although they were developed for adults, extrapolation to children using age-appropriate dosing seems reasonable, since the recommendations are already applied in many pediatric institutions. The guidelines are relatively safe, conservative, easy to follow, and, to some degree, take cost issues into account.

It is better for practitioners to administer drugs with which they are familiar than to give a different drug for each situation. Combining a primary technique with knowledge of what additions will do can optimize sedation and minimize the frequency of side effects. A method for evaluating the particular circumstance and developing an algorithm to adjust the sedation are also vital to effective sedation management. Future research should address some of these challenges faced by today's practitioners.

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