Abstract:
The spectrum of sedative and analgesic agents available to those who provide pediatric sedation and analgesia in the emergency department has broadened considerably over the past 2 decades. Pharmacologic agents that can be used alone or in combination in this context include nitrous oxide, midazolam, chloral hydrate, pentobarbital, etomidate, dexmedetomidine, propofol, and ketamine. The pharmacology, common clinical uses, advantages, and disadvantages of each of these agents are reviewed. Pharmacokinetics of the agents is addressed in tabular form, whereas pharmacodynamic aspects of each agent are discussed in more detail. Clinical uses addressed include noninvasive as well as invasive procedures. Relevant studies involving comparison of various sedative regimens for common emergency department procedures are reviewed.

Keywords:
procedural sedation; analgesia; pediatrics; chloral hydrate; dexmedetomidine; etomidate; ketamine; midazolam; nitrous oxide; pentobarbital; propofol

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Procedural Sedation and Analgesia in the Pediatric Emergency Department: A Review of Sedative Pharmacology

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The spectrum of agents available for pediatric procedural sedation and analgesia (PSA) in the emergency department (ED) has broadened considerably over the past 2 decades. The intramuscular narcotic-phenothiazine "cocktail" has been relegated to historical lore, and the present-day practitioner can choose from over a dozen pharmacologic options, enabling some finesse in matching the sedative-analgesic agents and routes of delivery to fit the clinical need.[1,2] The procedural sedation pharmacopeia can be divided into 4 main categories: pure analgesic, sedative-hypnotic, dissociative, and inhalational. The analgesics can be divided into opioid and nonopioid, and the sedative-hypnotic category can be further subdivided into benzodiazepines, barbiturates, and others (Figure 1). The agents can be used alone or in combination, further

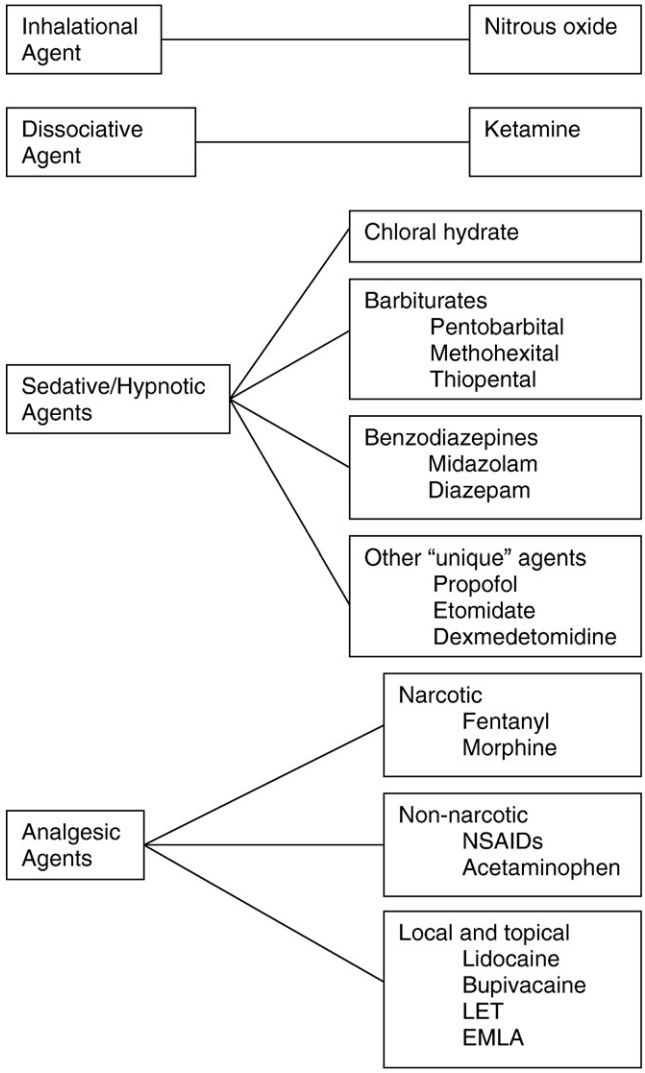

Figure 1. Pharmacopeia for procedural sedation and analgesia. EMLA - eutectic mixture of local anesthetic; LET - lidocaine, epinephrine, tetracaine; NSAIDs - nonsteroidal anti-inflammatory agents.

broadening the options for alleviating procedural pain and distress.

This article will review the pharmacology and clinical indications for commonly used sedative agents in present-day pediatric emergency medicine. Pharmacokinetics (how the body metabolizes the drug, including onset and duration) will be outlined in Table 1; the text will focus on sedative pharmacodynamics (how the drugs affect the patient), the common indications, and the advantages and disadvantages of each agent.

NITROUS OXIDE

Nitrous oxide (NO) is a gas that produces mild to moderate levels of analgesia, sedation, and dissociation when inhaled in concentrations of 30% to 70%.[3] Nitrous is administered with oxygen via 1 of 2 types of delivery systems, either fixed concentration (usually a 50:50 mixture) or titratable. The delivery system must include a scavenging mechanism to collect excess gas. Newer continuous-flow delivery systems alleviate the problem of the demand-valve mask, common in early systems designed for adult patients, which made use in the younger population difficult due to the inability to generate sufficient negative inspiratory pressure to open the valve. Systems with full face mask capability as compared to nasal hood only also expand the options for use in younger and less cooperative patients.

Nitrous oxide has been used in dental care settings for decades, and it has been recently undergoing a slow but steady increase in popularity for alleviating pain and distress for a variety of minor

invasive procedures in both ED and scheduled outpatient settings.[4-7] In particular, it has been useful for intravenous (IV) access procedures (vasodilatory properties are a helpful side effect),[8] bladder catheterization,[9] laceration repair,[10] and abscess drainage.[7] Local anesthesia is recommended as an adjunct for more painful procedures, as the analgesic properties of NO are modest in some patients.[11] When used with adequate local anesthetic, NO has been successful in alleviating pain in very painful procedures, including bone marrow aspiration and fracture reduction.[5,12] A recent evidence-based clinical policy deemed NO both safe and effective for pediatric PSA when used with concurrent local anesthesia, though the evidence quality is better for lower doses (50%) than for higher doses (up to 70%).[13]

The primary clinical advantage of NO is its very rapid onset and recovery, allowing its use at a moment's notice with return to baseline full function within 5 minutes. When used in lower concentrations (30%-50%), levels of sedation are unlikely to progress beyond mild sedation, and the typical regulatory requirements for moderate and deep sedation may be waived for lower concentration NO use.[4,7,14] However, nitrous is not completely free of risks. Adverse effects include nausea and vomiting in up to 10% of patients and dysphoria, restlessness, and headache in smaller percentages. Although delivery systems are improving, set up can still be cumbersome, and some patients do not cooperate well with inhaling from a mask. Nitrous oxide use is contraindicated in patients with risk of diffusion of gas into enclosed spaces, such as pneumothorax, pneumocephalus, or bowel obstruction. It has also been linked to increased risk of spontaneous abortion with chronic occupational exposure.

MIDAZOLAM

Midazolam (MDZ) is a benzodiazepine, a medication class (including diazepam and lorazepam, among others) with anxiolytic, amnestic, sedative-hypnotic, muscle relaxant, and anticonvulsant properties. Since its release in 1985, MDZ has far surpassed the other benzodiazepines for use in the PSA context due to its faster onset and offset, and to its water-soluble properties allowing administration via almost any route (intranasal, IV, oral, rectal, and intramuscular).[2] Intranasal administration causes significant stinging of the nasal mucosa, but onset of action is slightly faster than administration via enteral routes.[15] The IV formulation (5 mg/mL) can be used via any route; the commercially prepared oral formulation is less concentrated (2 mg/mL) and slightly more palatable than the IV formulation given orally. Like the other benzodiazepines, MDZ has no analgesic properties, and it should be administered with an analgesic for painful procedures. On a per-kilogram basis, larger doses are required for toddlers and young school-aged children compared to young infants and adolescents to achieve the same effect.

Midazolam alone is useful for "taking the edge off" an anxious or uncooperative child; however, when used as a single agent, it is unlikely to result in immobility, thus limiting its use in longer or more complex imaging studies. Ten percent of 516 children undergoing computed tomographic (CT) scans failed to achieve adequate sedation after 0.2 mg/kg of MDZ IV,[16] and half of 22 children randomized to 0.5 mg/kg of oral MDZ failed sedation for neuroimaging studies.[17] Midazolam has been used successfully, alone or in combination with topical or systemic analgesics, to provide adequate sedation for a wide variety of invasive procedures.[1] However, several comparison studies found MDZ alone or in combination with narcotics less desirable than newer "unique" short-acting sedatives and dissociative agents. In a blinded, randomized controlled trial of MDZ/fentanyl vs MDZ/ketamine for pediatric fracture reduction, MDZ/fentanyl was found to be less effective and to have a greater incidence of hypoxia (25% vs 6%) than MDZ/ketamine.[18] Another pediatric fracture reduction study found MDZ/morphine to be as effective as propofol/morphine; however, recovery times were an hour longer for the MDZ/morphine group.[19] Midazolam is often used as an adjunct with ketamine, though randomized placebo-controlled trials fail to show a clear benefit.[20]

The clinical advantages of MDZ include its versatility, beneficial spectrum of effects (including amnesia), and safety profile. When administered via incremental IV dosing, MDZ and MDZ/fentanyl combinations can be titrated to achieve truly moderate sedation, with the patient responsive to voice, more so than sedative regimens using dissociative or more potent sedative/hypnotic agents. However, MDZ has a synergistic respiratory depressant effect with narcotics and alcohol, and the practitioner using MDZ in combination with other respiratory depressants must monitor the patient with increased vigilance. Midazolam is well-known to produce dysphoria or agitation in a small percentage of patients, and the authors have found it helpful to warn parents ahead of time of the possibility of a paradoxical response. Both respiratory depression and paradoxical responses can be reversed with flumazenil.[21,22]

TABLE 1. Pharmacokinetics and dosing range for procedural sedation and analgesia agents

Drug	Effect	Dose	Onset (min)	Duration (min)	Reversible	Comments
Chloral hydrate	Sedative-hypnotic	PO/PR: 25-100 mg/kg Can repeat 25-50 mg/kg Max dose 2 g or 100 mg/kg Single use in neonates	10-30	30-120	No	Unreliable effects in >3 y, best if <10 kg, terrible taste, unpredictable onset and duration
Diazepam	Sedative-hypnotic	IV: 0.05-0.1 mg/kg titrated to max 0.25 mg/kg PO: 0.2-0.5 mg/kg PR: 0.2-0.5 mg/kg	IV: 4-5 PO: 15-30 PR: 5-15	IV: 60-120	Yes Flumazenil	Use lower doses if in combination with opioids; irritating to vein if given IV
Dexmedetomidine	Sedative-hypnotic Analgesic Anxiolysis	IV load: 1-2 μg/kg for 10 min; then 0.5-1 μg/kg per hour IN: 1-2 μg/kg	IV: 5-10 IN: 10-30	IV: 30-70 IN: 30-60	Yes, in theory Atipamezole (no published use in pediatric PSA)	Cardiorespiratory suppression Initial hypertension Use caution when administered with antisialagogue; avoid in patients on digoxin or other medications acting on the sinus node
Etomidate	Sedative-hypnotic	IV: 0.1 mg/kg titrated to effect	IV: < 1	IV: 5-15	No	Can cause respiratory depression, vomiting, myoclonus
Methohexital	Sedative-hypnotic	PR: 20-25 mg/kg IV: 0.5-1 mg/kg	PR: 10-15 IV: 1-2	PR: 30-60 IV: 15-30	No	Avoid in temporal lobe epilepsy and porphyria
Midazolam	Sedative-hypnotic, Anxiolysis	PO: 0.5-0.75 mg/kg PR: 0.25-0.5 mg/kg IN: 0.2-0.5 mg/kg IM: 0.1-0.2 mg/kg IV <5 y old: 0.05-0.1 mg/kg titrated to max 0.6 mg/kg IV >5 y old: 0.025-0.05 mg/kg titrate to max 0.4-0.5 mg/kg	PO: 15-30 PR: 10-30 IN: 10-15 IM: 5-20 IV: 1-3	PO: 60-90 PR: 60-90 IN: 15-60 IM: 60-120 IV: 45-60	Yes Flumazenil	Use lower dose if in combination with opioids May cause paradoxical excitement/irritability

Pentobarbital	Sedative-hypnotic	IV: 1-6 mg/kg titrated 1-2 mg/kg q2-5 min max 200 mg PO/PR <4 y old: 3-6 mg/kg titrated to max 200 mg PO/PR >4 y old: 1.5-3 mg/kg titrated to max 200 mg IM: 2-6 mg/kg max 200 mg	IV: 3-5 PO/PR: 15-60 IM: 10-15	IV: 15-90 PO/PR: 60-240 IM: 60-120	No	Younger children with paradoxical restlessness before sleep Avoid in porphyria
Propofol	Sedative-hypnotic	IV: 1 mg/kg titrated 0.5 mg/kg to effect IV infusion: 50-200 μg/kg per min	IV: < 1	IV: 5-15	No	Cardiorespiratory suppression Avoid with egg/soy allergies
Thiopental	Sedative-hypnotic	PR: 25 mg/kg	PR: 10-15	PR: 60-120	No	Avoid in porphyria
Fentanyl	Analgesic	IV: 1-2 μg/kg titrated 1 μg/kg q3-5 min	IV: 1-5	IV: 30-60	Yes Naloxone	Use lower dose if in combination with benzodiazepines Chest wall rigidity possible with IV push, especially in neonates
Morphine	Analgesic	IV: 0.05-0.15 mg/kg titrated to max 3 mg/kg	IV: 5-10	IV: 120-180	Yes Naloxone	Use lower dose if in combination with benzodiazepines
Ketamine	Dissociative sedative Analgesic Amnesic	IM: 4-5 mg/kg titrated to effect IV: 1-1.5 mg/kg titrated to effect PO: 5-10 mg/kg	IM: 3-5 IV: 1-2 PO: 15-30	IM: 15-90 IV: 15-30 PO: 30-60	No	Contraindicated in increased ocular pressure, psychosis, thyroid disease Emergence phenomenon
Nitrous Oxide	Inhalation sedative Amnesic Mild analgesia	Inhaled 30%-50% mixed with oxygen	1-5	<5	No	Must have specialized gas scavenger apparatus; caution in patients with entrapped gas (recent craniotomy, pneumothorax, bowel obstruction); avoid with methyltetrahydrofolate reductase mutations
Naloxone	Narcotic reversal	IM/IV: 0.1 mg/kg titrated to max 2 mg	IM: 10-15 IV: 2-3	IM: 60-90 IV: 20-40		Repeat doses needed if sedative is longer acting
Flumazenil	Benzodiazepine reversal	IV: 0.02 mg/kg titrated q 1 min to max 1 mg	IV: 1-2	IV: 30-60		Repeat doses needed if sedative is longer acting

IM indicates intramuscular; IN indicates intranasal, IV indicates intravenous, PO indicates per oral, PR indicates per rectum.

CHLORAL HYDRATE

Chloral hydrate (CH) is an alcohol-based sedative-hypnotic in use for pediatric procedural sedation for more than 100 years. Its use in this context has been reviewed extensively in a recently published clinical policy.[13] From an evidence-based perspective, CH is safe and effective (level A recommendations) for sedation in young patients (<3 years old) undergoing painless diagnostic studies, provided that the children are properly monitored. However, it is not recommended for use in this context in children older than 4 years, or in children with neurodevelopmental disorders, due to lack of efficacy.[13]

Advantages of CH include its extensive clinical history and its ability to reliably provide effective moderate to deep sedation, resulting in sleep and immobility in young children within the context specified above. Enteral administration increases its appeal in the chubby infant with poor IV access. Disadvantages, especially in a busy ED, include its relatively long and unpredictable onset (15-30 minutes, with 10%-25% of children requiring re-dosing after the first 30 minutes to induce sleep) and its long half-life. From the patient perspective, the biggest disadvantage is the bitter taste. Rectal administration is possible, although also unpredictable.

DEXMEDETOMIDINE

The newest agent on the pediatric procedural sedation scene is dexmedetomidine (DEX), a highly selective α-2 agonist with both sedative and analgesic effects, analogous to a faster-acting version of clonidine with fewer cardiovascular side effects. Dexmedetomidine can be delivered as an IV bolus/infusion, orally, or transmucosally via intranasal or buccal routes.

Published clinical uses for DEX to date include use as a preoperative premedication (before general anesthesia), as a long-term sedative in an intensive care unit setting, and as an adjunct sedative for invasive cardiology procedures. As an intranasal premedication, DEX was found to provide a slightly deeper sedation than oral MDZ, with a similar low rate of adverse side effects,[23] suggesting that it could serve as a less irritating substitute for ED procedures in which intranasal MDZ is considered. Indications more relevant to the ED setting include sedation for medical imaging procedures, both short (CT)[24] and long duration (magnetic resonance imaging [MRI]).[25] One recent publication suggests that DEX may be particularly useful in sedating autistic patients, in whom it was found to be effective with minimal recovery agitation for imaging and electroencephalographic procedures.[26] This population is not infrequently encountered in the ED and can be difficult to sedate with conventional means.

Advantages to DEX include multiple routes of administration, like MDZ, with better patient tolerance of the nasal and oral routes. Those who administer it frequently liken it to natural sleep, a belief borne out by electroencephalographic findings during DEX very closely resembling normal sleep.[27] Although ED experience is limited, DEX shows promise as a valuable addition to the sedation toolbox. An administrative advantage of DEX lies in its Food and Drug Administration labeling as a sedative as opposed to an anesthetic (unlike ketamine and propofol), thus potentially bypassing the need for approval by the anesthesia department in hospital systems where the ED sedation practice requires such approval. Dexmedetomidine is also potentially reversible with the α-2 adrenoreceptor antagonist atipamezole, with one report of success in adults[28] but no published use in children.

Disadvantages of DEX include its pharmacokinetics and hemodynamic side effects. From a pharmacokinetic standpoint, the onset and recovery times for DEX sedation are somewhat longer than propofol and ketamine but shorter than pentobarbital and chloral hydrate. Hemodynamically, DEX is known to cause an initial phase of hypertension with reflex bradycardia, followed by stabilization of both heart rate (HR) and blood pressure (BP) below baseline. In the high-dose DEX for MRI study by Mason et al,[30] 16% of the patient population had HRs below age-specific norms, and in 4% of patients, HR fell more than 20% below norms, although all patients maintained acceptable mean arterial BPs and recovered uneventfully. Care has to be taken with other agents acting on the sinus node, as severe sinus bradycardia has been reported with the combination of DEX and digoxin,[29] and Mason et al[30] reported several cases of exaggerated hypertension when glycopyrrolate was used to treat bradycardia in the setting of DEX infusions.

ETOMIDATE

Etomidate, an imidazole derivative, is an ultrashort-acting hypnotic sedative without analgesic properties that first appeared in ED practice as a favorable agent for rapid-sequence induction before tracheal intubation.[31] Deliverable only via IV, etomidate produces very potent sedation, anxiolysis, and amnesia, with minimal hemody-

namic effects, making it potentially desirable for procedural sedation.[2]

An evidence-based review found etomidate to be safe and effective for pediatric procedural sedation with level C recommendations, as initial publications of its use in this context were descriptive, retrospective studies.[1] Since that review, several randomized prospective trials using etomidate for pediatric PSA have been published. Etomidate/fentanyl was found to be more effective than MDZ/fentanyl for PSA in extremity fracture reduction, with shorter induction and recovery times.[32] A small randomized trial compared etomidate/fentanyl to ketamine/MDZ for fracture reduction and found higher pain scores but shorter recoveries with the former. Parents preferred the ketamine/MDZ combination despite the longer recovery times.[33] Etomidate was compared to pentobarbital for CT sedations in a large prospective, descriptive cohort study and was found to be both more effective and efficient than pentobarbital, with fewer complications.[34]

The advantages of etomidate include its rapid onset and recovery and the lack of effect on HR and BP. Rates of respiratory depression are similar to those of other sedative-hypnotics. The hemodynamic characteristics of etomidate increase its appeal for use in settings of potential cardiovascular instability, including sedation for electrical cardioversion of dysrhythmias, and for the trauma patient. However, etomidate is known to transiently suppress adrenal function via inhibition of 11 β-hydroxylase, which has been linked to adrenal insufficiency in a cohort of critically injured adults.[35] A definite causal link has not been established, and this transient adrenal suppression does not seem to cause problems in the routine sedation of healthier children. Other drawbacks of etomidate include pain on injection, nausea and vomiting, and potentially significant myoclonus. Myoclonus may be alleviated by the coadministration of low-dose midazolam.[36]

PENTOBARBITAL

Pentobarbital, along with its shorter-acting relatives methohexital and thiopental, is a barbiturate, a class of sedative known for profound sedation, hypnosis, amnesia, and anticonvulsant properties but no inherent analgesia. Barbiturates are in fact postulated to cause hyperesthesia and may increase pain sensation. Pentobarbital is typically delivered IV, whereas thiopental and methohexital have typically been delivered rectally, likely based on the very rapid effects achieved with transmucosal administration and potent respiratory depression when the latter are delivered IV. Pentobarbital can also be given orally, with a much longer time to onset.

Barbiturates have been used successfully for decades to provide procedural sedation in children, particularly for painless diagnostic imaging procedures. An evidence-based review found pentobarbital effective for producing cooperation for painless diagnostic procedures in children younger than 8 years, and safe, with the caveat that oxygen, positioning, and occasional positive pressure ventilation may be required (level B recommendations).[1] When compared to newer agents, however, pentobarbital has been found to be less effective and less efficient, with a higher rate of adverse effects, in particular vomiting and recovery agitation. Pentobarbital compared unfavorably to etomidate as described above.[34] Pentobarbital was also found to have much longer recovery times than propofol for MRI sedation in a small randomized controlled trial,[37] and pentobarbital was associated with higher rates of prolonged recovery, vomiting, and unplanned admission when compared to propofol for the same indication in a large descriptive cohort study.[38]

The advantages of pentobarbital sedation include decades of cumulative experience, with a relatively good efficacy and safety profile. Pentobarbital reliably produces deep sedation, and once a child reaches that point, they are likely to remain in "steady state" without further drug dosing or infusions of drug, for 30 to 90 minutes. However, the disadvantage of pentobarbital is that it may take anywhere from 5 to 15 minutes of irritability and "fighting sleep" to reach that steady state. Induction is often not smooth, particularly in toddlers. This irritability has led to the practice of adjunct medications, such as midazolam and fentanyl, being delivered along with pentobarbital, a practice that may contribute to prolonged sedation and that may not be necessary.[39] Other disadvantages of pentobarbital include respiratory depression, typically during induction of sleep, and nausea/vomiting and irritability, typically during recovery.

PROPOFOL

Propofol is a highly lipid-soluble, ultrashort-acting alkyl phenol agent with pure sedative properties. Although it provides no analgesia, it is capable of inducing a state of deep sedation allowing tolerance of painful procedures. It can only be administered IV and may be delivered as bolus doses for short procedures or via an infusion for longer ones.

Propofol is manufactured as a lipid emulsion that contains soy and egg lecithin, with the potential for allergic reactions in patients sensitive to soy or egg.[40] The lipid emulsion also promotes bacterial growth, and care must be taken to avoid contamination of the vial. It has a low pH and tends to burn when pushed. This injection pain can be ameliorated by coadministration with lidocaine, either IV lidocaine first to pretreat the vein or by mixing the two (1 part 1% lidocaine to 9 parts propofol).

Propofol has been in use as a general anesthetic since the 1970s. The first published use in a pediatric ED setting was in 1999, where it was shown to be an effective agent for fracture reduction.[19] Although controversy still exists in some institutions as to its appropriateness for use by nonanesthesiologists, the use of propofol in pediatric ED settings has expanded, and several published retrospective,[41,42] prospective,[43] and comparative studies have documented its safe and effective use in this setting. In addition, propofol has been shown to be more efficient and cost-effective than other procedural sedation regimens.[44] An evidence-based review found propofol effective for producing cooperation for painless diagnostic procedures (level C recommendations) and effective for painful procedures when combined with a narcotic (level B recommendations). Propofol was also deemed safe, with the caveat that oxygen, positioning, and occasional positive pressure ventilation may be required (level B recommendations).[1]

The advantages of propofol include its favorable pharmacokinetics, with very rapid onset and recovery, its effectiveness, and its low incidence of vomiting and other undesirable after effects. Disadvantages include its potential for respiratory depression, with transient hypoxia in 5% to 20% of patients, depending on the rate and amount of the initial bolus. Propofol also drops mean arterial BP by 10% to 25%, likely not significant in healthy children but potentially a problem in children with hemodynamic instability. Despite these disadvantages, its safe use by nonanesthesiologists has been documented in large cohorts of patients, with positive pressure ventilation required in 0.5% and tracheal intubation required in none of 1059,[45] and cardiopulmonary resuscitation required in 2 of 49 836 patients (both successful) as reported by the Pediatric Sedation Research Consortium.[46] The latter publication showed no difference in adverse events with propofol use between anesthesiologists and nonanesthesiologists in the centers reporting to the Pediatric Sedation Research Consortium, all of which have well-organized sedation systems.

Propofol also lacks analgesic properties. Although one can administer enough propofol to render a patient tolerant to painful procedures, this level of sedation may be considered general anesthesia. Other analgesics can be added to propofol for painful procedures. The addition of narcotics to propofol is common, although the combination may lead to increased respiratory and hemodynamic compromise. Propofol can be effectively combined with ketamine as these agents have complementary hemodynamic properties, and the "ketofol" combination may lead to less respiratory depression than propofol/fentanyl.[47-49]

Prolonged infusion of propofol has also been temporally linked to severe metabolic acidosis in intensive care unit settings, the so-called "propofol infusion syndrome,"[50] although this complication has not been reported in the setting of procedural sedation.

KETAMINE

Ketamine is a dissociative agent that produces a trancelike catatonic state with profound sedation, analgesia, and amnesia. As a noncompetitive *N*-methyl D-aspartate receptor antagonist, it works by blocking effects of excitatory amino acids on *N*-methyl D-aspartate receptors responsible for sensory perception, nociception, cognition, and consciousness. Ketamine is water soluble and lipophilic, allowing delivery via multiple routes.[51] Currently, the IV and intramuscular routes are most used given their effectiveness and reliability; however, ketamine can also be given orally,[52,53] rectally,[54] and intranasally.[55] At low doses, ketamine is primarily an analgesic with mild sedative properties. Higher doses produce the catatonic dissociative state; once this state is reached, additional doses will maintain but not "deepen" the level of sedation.[2]

First used in humans in the late 1960s, the use of ketamine for pediatric procedural sedation in the ED setting took off after a landmark series of articles published by Green et al[56-58] in the 1990s. It has since become one of the most popular and widely studied sedatives used for children in ED settings, used in 41% of all sedated procedures in a community ED sedation database.[59] Ketamine has been used successfully in a tremendous variety of procedures, including fracture reduction, laceration repair, arthrocentesis, incision and drainage, foreign body removal, central line or intraosseus needle placement, CT scan, hernia reduction, lumbar puncture, chest tube placement, eye examination, pelvic examination, paraphimosis

reduction, and rectal prolapse reduction.[58] It has become the gold standard to which other sedative regimens are compared, and it was the only parenteral sedative in an extensive evidence-based review of pediatric sedation to receive level A recommendations for safety and efficacy.[1]

Ketamine is unique among the commonly used sedatives in that respiratory drive and airway reflexes are maintained although the patient has been rendered unresponsive. Another advantage is its mild bronchodilatory effect, making it a desirable choice for sedation in the asthmatic patient. A randomized controlled trial of subdissociative dosing of ketamine failed to show a difference in asthma recovery,[60] but case series reports using higher doses did report an effect.[61,62] Because of the potential for laryngospasm (0.4% of patients in one large series),[58] ketamine use in intraoral procedures was initially discouraged, although it has been used successfully with dental procedures[63] and peritonsillar abscess drainage.[64] In addition to laryngospasm, potential side effects include airway malalignment, excessive salivation, transient respiratory depression (especially if it is pushed quickly via IV), tachycardia, and hypertension. A large meta-analysis failed to note a benefit of antisialagogue use with ketamine, and in fact linked antisialagogue use to a slight increase in adverse respiratory events, although confounding bias could not be eliminated.[65]

Another effect of ketamine is catecholamine-mediated increase in HR and blood pressure, associated with increased intracranial and intraocular pressure. These effects are well tolerated in healthy children but have led to restrictions in the use of ketamine in patients with cardiac disease, brain injury, or elevated intracranial pressure. Recent literature raises questions about these restrictions, as ketamine has been used successfully for sedation for cardiac catheterization in patients with congenital heart disease[66] and in patients with documented elevated intracranial pressure. In a cohort of intensive care unit patients with intracranial monitors in place, ketamine sedation actually lowered intracranial pressure.[67]

Ketamine is also notorious for emergence phenomena and vomiting during recovery, reported in 5% to 15% of patients in a large meta-analysis. Contrary to initial beliefs, emergence phenomena are not age related and are not affected by the coadministration of benzodiazepines.[68] Parents and patients should be notified in advance of the common visual side effects of nystagmus and double vision. Double vision and visual hallucinations are common during recovery and may contribute to emergence agitation. Vomiting after ketamine administration peaks in the young adolescent age groups and is more common with intramuscular or high-dose (>2.5 mg/kg) IV administration. Administration of ondansetron may alleviate the vomiting.[69]

Ketamine use is contraindicated in children younger than 3 months due to increased apnea risk and in patients with suspected or known psychosis. Relative contraindications include children younger than 12 months and in patients with hyperthyroidism or porphyria.[2]

SUMMARY

Emergency medicine physicians caring for children can choose from multiple pharmacologic agents that are capable of creating safe and effective procedural conditions in the ED, either alone or in combination. Clinicians should become familiar with these agents, their pharmacokinetics, pharmacodynamics, and availability in their own practice environments, to alleviate procedural distress whenever possible.

Future directions in sedation pharmacology will likely bring refinements in the drugs themselves, as well as an increased understanding of the patient's response to the drugs, in part through the burgeoning field of pharmacogenetics.[70] Further understanding of the effect of sedative and anesthetic agents on the developing brain is also forthcoming, as current investigations are underway to evaluate the potential for neuroapoptosis in young infants with the use of commonly used sedatives such as ketamine and propofol.[71] In addition to sedative effects in young infants, research is also progressing on the use of sedatives for other specific patient populations, such as cardiac patients.[72] Emergency medicine physicians have been and will continue to be integrally involved in advancing pediatric procedural sedation.

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