A Review of Current Oral Sedation Agents for Pediatric Dentistry

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The administration of oral sedatives for minimal and moderate sedation is common practice for pediatric dentistry. Being up to date with contemporary medications and dosing recommendations is imperative for patient safety. Historic medications such as chloral hydrate have become obsolete with the introduction of benzodiazepines and other newer medications such as alpha-2 adrenergic agonists. Oral opioids are useful for analgesia and mild sedation but may result in significant respiratory depression when combined with other central nervous system depressants and, if left untreated, hypoxemia. Antihistamines can provide minimal sedation but may have other added benefits such as antiemetic and antisialagogue effects. This review will discuss relevant pharmacologic aspects, including onset, duration of action, metabolism, and adverse reactions, for several common agents used for minimal and moderate oral sedation to assist practitioners in determining ideal medications or combinations that fit the needs of the pediatric patient and dental procedure contingent upon the provider's level of training.

Key Words: Pediatric oral sedation; Sedation dentistry; Chloral hydrate; Benzodiazepines; Opioids; Antihistamines; Alpha-2 adrenergic agonists; Dexmedetomidine; Zolpidem; Melatonin.

Several trends and various combinations of medications have been used for minimal and moderate enteral sedation in pediatric dental patients. A variety of factors, such as efficacy, safety records, patient acceptance, and the development of novel and more widely accepted medications, have expanded the envelope of available agents in use today. Various medications administered orally can act on gamma-aminobutyric acid (GABA), opioid, histamine (H1), or alpha-2 adrenergic receptors within the central nervous system (CNS) to produce sedative effects with the intent of decreasing excitability and physical activity while also creating a calming effect prior to dental treatment (Tables 1 and 2). In addition, drugs with sedative and/or hypnotic effects can also be used with the intent of producing drowsiness or somnolence.[1] Understanding the key differences between various drug classes and available oral sedatives is imperative when developing an anesthetic plan that fits the needs of the patient and dental procedure. This review will discuss some of the common historical medications along with more contemporary agents used for minimal and moderate enteral sedation in pediatric dentistry.

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CHLORAL HYDRATE

Chloral hydrate, a sedative-hypnotic aldehyde compound used in the late 1800s for insomnia, was once the predominant agent for oral sedation in children. Once absorbed by the gastrointestinal (GI) tract, chloral hydrate is metabolized by alcohol dehydrogenase in the liver and converted to trichloroethanol, which is the active drug form with similar effects to ethanol. Although not explicitly clear, it is presumed that chloral hydrate exerts its effects via positive allosteric modulation involving $GABA_A$ receptors much like barbiturates and benzodiazepines.[1,2] The onset of action typically occurs within 30 to 60 minutes. The duration of action of chloral hydrate approximates 4 to 8 hours, with trichloroethanol having a beta/elimination half-life of approximately 8 to 11 hours.[3,4]

Chloral hydrate can be irritating to the gastric mucosa, often resulting in nausea and vomiting. Because of its bitter taste, it has relatively poor patient acceptance and tolerability during oral administration. Large doses can cause the myocardium to become overly sensitized to epinephrine.

Table 1. Common Pediatric Oral Sedation Medications

Drug	*Pediatric dosing*	*Onset*	*Duration*	*Half-life*	*Reversible*	*Formulations*	*Side effects*	*Notes*
Chloral hydrate	20–25 mg/kg	30–60 min	60–120 min	8–11 h	No	Cap: 500 mg Syr: 500 mg/5 mL	Nausea, respiratory depression	Sensitizes myocardium to epi
Diazepam	0.2–0.5 mg/kg, max 10 mg	30–45 min	60–180 min	24–72 h	Yes	Tab: 2, 5, 10 mg Sol: 5 mg/mL	Nausea, respiratory depression	Avoid with glaucoma, active metabolites
Midazolam	0.25–0.5 mg/kg, max 20 mg	15–30 min	0.5–2 h	1–2 h	Yes	Sol: 1, 5 mg/mL Syr: 2mg/mL	Respiratory depression	Avoid with glaucoma, bitter taste
Meperidine	1.1–1.8 mg/kg	15–20 min	60–100 min	3–5 h	Yes	Tab: 50 mg Sol: 50 mg/5mL	Nausea, respiratory depression, histamine release	Avoid with MAOI and seizures
Morphine	0.2–0.5 mg/kg	15–30 min	3 h	3–5 h	Yes	Sol: 10, 20 mg/5 mL	Nausea, respiratory depression, pruritis	Active metabolites

Cap, capsule; epi, epinephrine; MAOI, monoamine oxidase inhibitors; Sol, solution; Syr, syrup; Tab, tablet.

While capable of producing acceptable levels of sedation especially when used in combination with other agents, chloral hydrate notably lacks any major analgesic effects. Patients have become delirious or combative during painful or stimulating dental procedures, such as a tooth extraction or seating a stainless-steel crown, following solo use of chloral hydrate.[2]

Serious life-threatening complications have been reported with chloral hydrate including laryngospasms, cardiac arrhythmias, cardiac arrest, and seizures.[3] Cote et al[5] implicated its use as contributory factor for poor outcomes in an oft-cited study on pediatric adverse sedation events published in 2000. Most importantly, chloral hydrate has no reversal agent to counteract the effects of sedation levels deeper than intended (eg, cardiac and respiratory depression).

While this was once a popular medication, it has been supplanted by short-acting benzodiazepines and other agents. Sheroan et al[3] demonstrated similar success rates in triple-drug cocktails comparing chloral hydrate, meperidine, and hydroxyzine vs midazolam, meperidine, and hydroxyzine. Chloral hydrate is no longer commercially available and is on formulary at only some compounding pharmacies in the United States (US). Dosing recommendations are 50 to 100 mg/kg; however, deaths have occurred even within this range.

BENZODIAZEPINES

Benzodiazepines are commonly used for minimal and moderate oral sedation for pediatrics. These medications can be administered not only orally but also parenterally, such as via the intranasal (IN), intramuscular (IM), and intravenous (IV) routes. For this review, the scope of discussion will be limited to oral administration. The chemical structure of benzodiazepines includes a benzene ring fused to a 7-membered diazepine ring.[1] Benzodiazepines exert their positive allosteric modulatory effects by binding to specific receptors, the aptly named benzodiazepine binding site, located within the $GABA_A$ complex. GABA is the main endogenous inhibitory neurotransmitter within the CNS, and benzodiazepines potentiate its inhibitory effects. $GABA_A$ receptors are ligand-gated chloride channels found within in the CNS,[1,2] and rather than opening the ion channels directly, benzodiazepines act as positive allosteric modulators to facilitate the binding of GABA to its respective 2 receptor sites. The net result of this action is the influx of chloride into the cell, which negatively hyperpolarizes the neuron and limits excitatory signaling.[2]

Lipid solubility and clearance are 2 key features that largely distinguish between different benzodiazepines.[1,2] Lipid solubility is important when deciding what drug to administer as it affects drug onset and duration of action. Generally, the higher the degree of lipid solubility, the faster the onset of action due to increased absorption and

Table 2. Antihistamine Adjuncts for Oral Sedation

Drug	*Dosing*	*Onset*	*Duration of action*	*Side effects*	*Notes*
Diphenhydramine	Peds: 1 mg/kg/dose Adult: 25–50 mg daily, max 300 mg	15–60 min	3–4 h	Dry mouth, dizziness, headache, blurred vision	Safe for pregnancy, avoid with closed angle glaucoma and hyperthyroid
Doxylamine	Peds: 2–6 y: 2–3.125 mg, 6–12 y: 3.75–6.25 mg, >12 y: 5–10 mg Adult: 5–10 mg	30 min	6 h	Dry mouth, dizziness, headache, blurred/double vision	Safe for pregnancy, antitussive, antiemetic,avoid with HTN
Hydroxyzine	Peds: 0.6 mg/kg, max 25 mg/dose Adult: 50–100 mg	15–60 min	60 min	Dry mouth, dizziness, headache	Avoid with HTN and stenosing peptic ulcer
Promethazine	Peds: 1 mg/kg, (usually, 12.5–25 mg) Adult: 25–50 mg	15–60 min	4–6 h	Dry mouth, drowsiness listlessness, blurred/double vision	Useful for nausea, vomiting, and motion sickness; BLACK BOX UNDER 2 y

BLACK BOX, US FDA black box warning for use in patients under 2 years of age; HTN, hypertension.

diffusion across the lipophilic blood-brain barrier.[2] The duration of action will be shorter as the drug redistributes away from the brain and into inactive sites (ie, adipose tissue). Clearance is important because it affects the duration of action as well as time to recovery. Most benzodiazepines undergo hepatic phase 1 reactions via the cytochrome P450 (CYP) enzymes CYP3A4 and CYP2C19: demethylation, hydroxylation, and oxidation.[2] Drug metabolism and elimination can further be affected if the patient suffers from hepatic or renal disease.

Clinical effects produced by benzodiazepines include sedation, hypnosis, anxiolysis, muscle relaxation, anterograde amnesia, and anticonvulsant effects to varying degrees.[1,6,7] Similar to most sedative-hypnotics, benzodiazepines do not provide analgesia and, in fact, lower the pain threshold. Many benzodiazepines have US Food and Drug Administration (FDA) approval for the treatment of delayed sleep onset and sleep-maintenance insomnia. The therapeutic index (toxic/therapeutic dose ratio) for benzodiazepines is very high. Most have a published dosing ranges significantly higher than usually administered to pediatric patients for moderate enteral sedation to produce significant adverse effects.[2] This drug class is widely safe and is only relatively contraindicated in most cases with few absolute contraindications. Benzodiazepines can also cross the placenta and are secreted in breast milk.[1] Common side effects include headache, blurred vision, hiccups, vertigo, and paradoxical reactions.[1,8]

In terms of the clinical goals of sedation, benzodiazepines are fairly equal regarding predictability. However, they can vary in the degree and duration of anterograde amnesia produced. When a benzodiazepine is used for moderate sedation, it is possible for a patient to respond normally or purposefully in the moment but lack any recollection postoperatively.[2] At recommended doses for minimal and moderate sedation (ie, anxiolysis) and when used as the single sedative agent, benzodiazepines have minimal effect on respiratory or cardiovascular function.[1,2,6] At doses used for deep sedation and general anesthesia, respiratory depression along with hypoxemia and hypercapnia is potentiated through a reduction in chemoreceptor responsiveness.[1]

In addition, benzodiazepines can lead to indirect muscle relaxation. Relaxation of the skeletal muscles can be most readily appreciated as upper airway muscle tone decreases, potentially resulting in partial or complete airway obstruction. This effect can be magnified and have serious unintended consequences in patients with chronic obstructive pulmonary disease or obstructive sleep apnea.[1,2]

Midazolam

Midazolam is one of the most lipid-soluble benzodiazepines, resulting in a very rapid onset, shorter duration of

action, and high degree of amnesia.[2,3] Midazolam is 2 to 5 times as potent as diazepam as it has a higher affinity for the benzodiazepine receptor in the brain.[6] Due to degradation in the stomach, absorption, and first-pass metabolism, it has an oral bioavailability of only 50% to 65%.[6] Onset after oral administration typically occurs within 20 to 30 minutes, and its duration of action approximates 30 minutes up to 2 hours depending on the dose. It has an elimination half-life of roughly 1 to 4 hours.[3,6,9]

Midazolam is commercially available in a concentrated syrup (2 mg/mL); however, IV formulations can also be used when mixed with a variety of flavorings or syrups. Dosing of orally administered midazolam has been heavily studied, with formulations including the 2 mg/mL syrup as well as the 1 and 5 mg/mL IV solutions. Unwillingness to accept orally administered midazolam is a predictor for sedation failure.[8] Current dosing recommendations for oral conscious sedation are 0.25 to 0.5 mg/kg, with a maximum dose of 20 mg.[9]

Paradoxical reactions have occurred and been reported in a small number of patient populations.[10] Vaskova et al[10] reported the frequency of such paradoxical reactions to range between 1% and 2% and decrease in frequency according to age. Characteristics of this midazolam-induced paradoxical reaction include restlessness or agitation to anger, hostility, and violence.[11] In addition, the additive and synergistic effects of midazolam combined with other sedative medications, such as antihistamines, opioids, and the inhaled CNS depressant nitrous oxide, can lead to clinically significant sedation beyond intended levels.

Diazepam

Prior to the advent of midazolam, diazepam was often used in pediatric dentistry. Diazepam undergoes hepatic metabolism and has the notable active metabolites temazepam, oxazepam, and nordiazepam (desmethyldiazepam).[2] Desmethyldiazepam is largely responsible for the resedation or drowsiness that can occur hours after administration.[6] Prolonged clinical sedation occurs via enterohepatic circulation, where active metabolites of diazepam are stored in bile and released back into enteric circulation.

Cardiovascular effects of diazepam are secondary to a reduction in left ventricular function, causing a decrease in cardiac output.[1] Diazepam also increases coronary blood flow. After oral administration, less than 90% of the drug is absorbed.[7] Time to peak concentration is 15 to 30 minutes in children when fasting,[6,7] and its distribution half-life approximates 1 hour but can range up to more than 3 hours. Metabolism occurs via CYP3A4 and 2C19 hepatic enzymes.[7] Due to its long elimination half-life of 21 to 37 hours, increased attention must be paid with diazepam given its potential for resedation and airway obstruction—especially in obese patients when administered in conjunction with opioids.[6] Diazepam is contraindicated in myasthenia gravis, severe respiratory insufficiency, and sleep apnea.[7] It is available in oral formulation as 2-, 5-, or 10-mg tablets or as a 5-mg/mL solution.[6] The typical dosing is 0.2 to 0.5 mg/kg, up to 10 mg.

Benzodiazepine Reversal

Flumazenil. Flumazenil is the singular member of its own drug class, an imidazobenzodiazepine.[2] It has high affinity for the $GABA_A$ receptor, where it acts as a competitive antagonist to the benzodiazepines and the nonbenzodiazepines, reversing effects such as somnolence and respiratory depression.[1] Flumazenil itself has no active properties and can reverse even the benzodiazepine inverse-agonist actions (anxiety, arousal, and convulsions) of methyl beta-carboline carboxylate. Prior to or during the administration of this antagonist, it is important to assist a patient suspected of symptomatic benzodiazepine oversedation with supplemental oxygen and airway rescue maneuvers (eg, a head tilt or chin lift) rather than delay such critical interventions unnecessarily. Flumazenil is contraindicated in patients with a history of seizure or chronic anxiety disorders where benzodiazepines are used to manage the condition.

Flumazenil undergoes hepatic metabolism to inactive metabolites with an elimination half-life of approximately 1 hour.[1] It is rapidly redistributed and exhibits typical 2-compartment pharmacokinetic behavior. Rapid distribution is followed by a predominant phase of metabolism by ester cleavage with almost complete transformation by CYP3A4 isoenzymes into inactive carboxylic acid and glucuronide forms.[12]

There is no evidence to support the routine use of flumazenil at the end of a procedure to accelerate or provide safer patient recovery and discharge. Flumazenil is available in a 0.1-mg/mL concentration in 5- or 10-mL vials. IV administration is recommended at 0.01-mg/kg (max of 0.2 mg) increments every 60 seconds up to a total of 0.05 mg/kg or 1 mg, whichever is lower.[2,6,9] The duration of reversal ranges from 20 to 60 minutes, so it is imperative that the rescued patient be monitored for longer than that period, as resedation is possible.

OPIOIDS

Opioids provide both analgesia and sedation through agonistic action involving central and peripheral mu, delta, and kappa opioid receptors.[2,9] Common and serious side effects of opioids include clinically significant respiratory

depression, nausea, vomiting, delayed gastric emptying, constipation, and pruritis. Opioids produce respiratory depression via direct action on the ventilatory control center in the medulla and blunt the response to hypercarbia and hypoxemia, raising the apneic threshold.[6] Opioids induce nausea and vomiting via action on the chemoreceptor trigger zone in the area postrema.[6] When combined with benzodiazepines or other CNS depressants, synergistic action can potentiate profound respiratory depression that can lead to hypoxemia. Anesthesia and sedation techniques using Enhanced Recovery After Surgery principles tend to minimize or eliminate their use during the procedure and postoperative recovery periods to minimize the negative side effects of opioids.[13]

Meperidine

Meperidine is a synthetic opioid agonist belonging to the phenylpiperidine class and a potent mu receptor agonist. It may produce less smooth muscle spasm, constipation, and depression of the cough reflex than equivalent doses of morphine. It has a rapid onset of action, slightly more rapid than morphine, and an intermediate duration of action, which makes it a desirable medication for longer dental procedures.[14] Meperidine is well absorbed from the GI tract and reaches its peak effect in roughly 60 minutes.[6] Approximately 90% of enterally administered meperidine undergoes biotransformation via first-pass N-demethylation to normeperidine and meperidinic acid primarily by CYP2B6, CYP3A4, and CYP2C19.[6] The active metabolite normeperidine provides approximately 50% of the analgesic activity of meperidine and is neurotoxic,[15] with accumulation precipitating seizures.[1]

Meperidine can also be administered IV, IM, and subcutaneously. For oral administration, meperidine is available as a 50-mg tablet or a 50-mg/5-mL solution. Pediatric oral administration dosing is usually 1.1 to 1.8 mg/kg, not to exceed 100 mg when given alone or 50 mg when used in combination with other CNS depressants.[6] Meperidine is rarely used as a singular agent for pediatric oral sedation and quite frequently used in conjunction with benzodiazepines, antihistamines, and inhaled nitrous oxide.[16]

Morphine

Morphine is another potent mu receptor agonist that provides analgesia for moderate to severe pain. As the baseline to which all other opioids are compared in terms of potency, morphine has been historically used for analgesia. Morphine has gained popularity in some oral sedation regimens mainly due to its lack of neurotoxic metabolites as compared with meperidine.

Morphine is metabolized via glucuronidation into morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). The liver is the major site of metabolism of morphine, but evidence of extrahepatic glucuronidation has been reported.[17] Opioid effects attributed to M6G develop with a remarkable delay from the rise of M6G plasma concentrations caused by slow and incomplete transfer of M6G through the blood-brain barrier; therefore, results may be variable after oral administration.[11] In contrast to M6G, M3G shows no affinity for the mu and delta opioid receptors and is presumed to be devoid of analgesic activity. M3G has been shown to produce behavioral excitation, myoclonus, and seizures.[11] Respiratory depression is the primary risk with morphine administration, but other side effects include nausea, vomiting, constipation, dizziness, and itching.

Chen and Tanbonliong reported the use of "triple cocktails" in a retrospective study comparing oral morphine, midazolam, and hydroxyzine vs oral morphine, diazepam, and hydroxyzine in 271 pediatric patients undergoing various dental procedures.[18] Their results demonstrated an 80% success rate with minimal airway compromise that was corrected with a chin lift.

Morphine is available as an oral formulation as either 10 or 20 mg/5 mL (2 or 4 mg/mL). Attentiveness is imperative when formulating and administering morphine solutions if different concentrations are kept in the same location to prevent inadvertent dosing, overdose, or death. The onset of oral morphine by the oral route is approximately 20 to 40 minutes, with a time to peak analgesia of 60 to 90 minutes and a duration of 3 to 6 hours. The oral bioavailability of morphine is approximately 35% with a half-life of 1.5 to 4.5 hours.[11] Typical pediatric oral dosing is 0.2 to 0.5 mg/kg. Like meperidine, morphine is also generally not used singularly but rather in combination with other agents.

Opioid Reversal

Naloxone. Naloxone is a semisynthetic, pure competitive opioid antagonist with a high affinity for mu opioid receptors, allowing for full opioid reversal.[6] Its onset of action varies depending on the route of administration but can be as rapid as 1 minute when delivered via the IV or intraosseous route. Naloxone has an elimination half-life of 30 to 120 minutes with a typical reversal time of 45 minutes.[6,19] Because the duration of action of most opioids often exceeds the duration of action of naloxone, close observation and monitoring of the patient are necessary after naloxone administration to watch for signs of resedation and respiratory depression. Although unlikely in pediatric oral sedation situations for dental care, rapidly reversing excessive opioid administration can precipitate nausea and vomiting, diaphoresis, hypertension, cardiac

dysrhythmias, and pulmonary edema, particularly for patients dependent on opioids.[6]

IN naloxone nasal spray has been shown to be effective and safe in both pediatric and adult populations. The IN spray is supplied as 4 mg of naloxone hydrochloride in 0.1 mL. A single spray should be given intranasally to adults or pediatric patients who are unresponsive or experiencing respiratory depression where there is suspicion of opioid overdose.

For use in pediatric dental settings where IV access or IM administration may be limited, the IN route may be the most rapid and practical method of delivering rescue from opioid-induced respiratory depression and hypoxemia. Like any pharmacologic reversal strategy, IN naloxone should also be accompanied by the activation of emergency medical services, summoning additional help, airway rescue, and supplemental oxygen. Additional doses of naloxone nasal spray may be given using additional nasal spray units with successive doses if patient does not respond. Alternating nostrils should be used every 2 to 3 minutes until emergency medical assistance arrives.[20]

ANTIHISTAMINES

Although antihistamines do provide some degree of sedation, they are typically not recommended as primary sedative medications as the degrees of anxiolysis and sedation are minimal relative to benzodiazepines. Sedative antihistamines cross the blood-brain barrier and provide sedation through antagonism of the hypothalamic histamine (H1) receptors.[2] H1 receptors are also found on the respiratory smooth muscles, GI tract, cardiac tissues, immune cells, uterus, and within the CNS.[21]

Because antihistamines work on different receptors than other sedatives, they allow for a multimodal approach potentiating minimal and moderate sedation without the risk of major respiratory depression when used within recommended dosing ranges. An added benefit with antihistamines is their anticholinergic and antiemetic effects. The antiemetic effects are most evident with promethazine; however, all of the antihistamine agents discussed here display anticholinergic effects including antisialagogue effects, increased heart rate, and slowed GI motility.

Diphenhydramine

Available as an over-the-counter medication, diphenhydramine is a first-generation antihistamine. Diphenhydramine has been used in the treatment of pruritis, urticaria, vertigo, motion sickness, insomnia, and dystonia prevention.[15] It functions as an inverse agonist at the H1 receptor, a competitive antagonist at the muscarinic acetylcholine receptor, and intracellularly as a sodium channel blocker.[15]

Diphenhydramine is metabolized primarily by CYP2D6 N-demethylation and has an elimination half-life of 3.4 to 9 hours and oral bioavailability of 40% to 60%.[6,15] It has a potential for prolonging the cardiac QT interval. It can be administered topically, orally (via tablet, capsule, or solution), or the IM and IV routes. Pediatric dosing of 1 mg/kg/dose or 25 to 50 mg/dose in older patients will yield an onset of 15 to 60 minutes with a duration of action up to 3 hours depending on the route of administration.

Doxylamine

Doxylamine is an antihistamine commonly used as a sleep aid. This drug is also used to relieve symptoms of hay fever (allergic rhinitis), hives (rash or itching), and other allergic reactions. Doxylamine, used in combination with vitamin B6, is a common treatment for nausea and vomiting associated with early pregnancy ("morning sickness").[22] Doxylamine is a member of the ethanolamine class of antihistamines and has antiallergy power far superior to virtually every other antihistamine on the market, with the exception of diphenhydramine.[23] It is the most powerful over-the-counter sedative available in the US and is more sedating than many prescription hypnotics.[16] In one study, it was found to be superior to even the barbiturate phenobarbital for use as a sedative.[16] Doxylamine is also a potent anticholinergic.[16]

The drug undergoes extensive hepatic metabolism by CYP450 and is excreted primarily in the urine.[17] It has a half-life of approximately 10 hours, which increases to 12 to 15 hours in the elderly.[24] Safety and efficacy have not been established in patients younger than 12 years, and it is advised not to use doxylamine in children under the age of 2.[17] Fatalities have been reported from doxylamine overdose in children. The overdose cases have been characterized by coma, grand mal seizures, and cardiorespiratory arrest.[25] Children appear to be at a high risk for cardiorespiratory arrest.[18] A toxic dose for children of more than 1.8 mg/kg has been reported.[18]

Hydroxyzine

Hydroxyzine is another first-generation histamine H1-receptor antagonist of the diphenylmethane and piperazine classes that exhibits sedative, anxiolytic, anticholinergic, and antiemetic effects.[6,26] Its mechanism of action is inhibition of the H1 receptors in the hypothalamus, which modulates sleep-wake cycles.[6] Of the antihistamines used in oral sedation for pediatric dentistry, hydroxyzine is the most popular, with numerous studies evaluating its efficacy and safety when used alone or in combination with other

agents. As an antisialagogue mediated by moderate anticholinergic effects, hydroxyzine is useful in dentistry for promoting a dry operative field and reducing secretions that can lead to airway compromise and laryngospasm.

Hydroxyzine is metabolized by CYP3A4 and CYP3A5. Its main and active metabolite (~45%–60% of the orally administered dose) is the second-generation antihistamine cetirizine, which is generated by oxidation of its alcohol moiety to a carboxylic acid.[27] Hydroxyzine is relatively fast acting with an onset that occurs between 15 and 60 minutes and a duration of action between 4 to 6 hours. The sedative properties of hydroxyzine occur at the subcortical level of the CNS.[19]

Hydroxyzine is reported to prolong the QT/QTc interval based on postmarketing reports of rare events of torsade de pointes, cardiac arrest, and sudden death and should be used with caution in patients with an increased baseline risk for QTc prolongation properties.[19] Pediatric dosing is 0.6 mg/kg, up to 25 mg/dose, and it often used a singular agent or in combination with inhaled nitrous oxide and other CNS depressants.

Promethazine

Somewhat of an outlier in the antihistamine category is promethazine, a first-generation antipsychotic with moderate antihistaminergic action. It has multireceptor activity as an antagonist of histamine H1, postsynaptic mesolimbic dopamine, alpha adrenergic, muscarinic, and N-methyl-D-aspartate (NMDA) receptors.[6] Its antihistamine action is used to treat allergic reactions, while its antagonism of muscarinic and NMDA receptors contribute to its use as a sleep aid as well as for reducing anxiety and tension. Antagonism of histamine H1, muscarinic, and dopamine receptors in the medullary vomiting center make promethazine useful for treating nausea and vomiting.[28] Patients should be counseled regarding CNS and respiratory depression with therapeutic dosing along with reductions in seizure thresholds and bone marrow depression if applicable. Antidopaminergic actions of this drug can also precipitate extrapyramidal reactions, pseudoparkinsonian tremor, and tardive dyskinesia in susceptible patients, and its anticholinergic action can cause xerostomia, increases in heart rate, blurred vision, and constipation/urinary retention.

Promethazine's peak plasma time is 2 to 3 hours after oral administration, and its therapeutic effects generally last 4 to 6 hours but can persist up to 12 hours. Promethazine is metabolized principally to promethazine sulfoxide and to a lesser degree desmethylpromethazine with the major site of metabolism being the liver, and it is subjected to extensive first-pass hepatic biotransformation by CYP2D6,[29] resulting in an oral bioavailability of approximately 25%.[21]

Postmarketing cases of respiratory depression, including fatalities linked to sudden infant death syndrome, have been reported with use of promethazine.[21] Because of this, the US FDA has placed a black box warning for promethazine use in children younger than 2 years. In a randomized, crossover clinical trial by Mozafar et al,[30] 18 uncooperative children requiring dental work were given either 50% nitrous oxide with 0.5 mg/kg of oral midazolam or 50% nitrous oxide with 1 mg/kg of promethazine. The study demonstrated that children sedated by the midazolam group expressed lower anxiety during the treatment in comparison with children in the promethazine group ($P < .05$).[30] Typical dosing is 1 mg/kg, which generally equates to a 12.5- or 25-mg tablet for most children, and promethazine is most often used in combination as an adjunct to another primary oral CNS depressant.

ALPHA-2 AGONISTS

Alpha-2 adrenergic agonists are a drug class that is gaining favor in oral sedation for pediatric dentistry. Their mechanism of action involves a sympatholytic effect mediated by reduced presynaptic norepinephrine release from central and peripheral sympathetic neurons.[31] Centrally, these drugs modulate vasomotor centers, resulting in decreased sympathetic outflow and increased parasympathetic tone from the locus coeruleus.[32,33] Sedation, analgesia, and rapid eye movement sleep are achieved through modulation of the locus coeruleus, which causes increased inhibition of GABAergic neurons. Meanwhile, analgesia is achieved through alpha-2 adrenergic activation in the brain, dorsal horn, and peripheral nerves.[24] Peripherally, alpha-2 adrenergic agonists exhibit vagolytic activity by blocking chronotropy while also vasodilating via direct action on the alpha-2 adrenergic receptors in smooth muscle cells.[24]

Alpha-2 adrenergic agonists can influence and reduce the transmission of pain within the spinal cord where norepinephrine is released from the descending inhibitory bulbospinal neurons and bind to alpha-2 adrenergic receptors in the dorsal horn. Interference of norepinephrine's effects on these spinal receptors results in a decrease in afferent pain transmission and produces analgesia.[25] Hypotension and bradycardia are the most common adverse events and are more common with continuous IV infusions. Overall, alpha-2 adrenergic agonists provide a relatively safe hemodynamic, respiratory, and pharmacologic profile that provides clinically relevant sedation without significant respiratory depression.[23]

Clonidine

Originally intended as an antihypertensive agent, clonidine received US FDA approval for the treatment of attention-

deficit hyperactivity disorder in pediatric patients in 2010. It can be administered intravenously, orally, neuraxially, or transdermally. Clonidine is available in oral formulation in 0.1-, 0.2-, and 0.3-mg tablets. Effects are seen at 30 to 60 minutes after oral ingestion with peak effects at 2 hours.[25] The elimination half-life of clonidine is 12 to 24 hours[23] with hydroxylation occurring with CYP2D6, 1A2, 3A4, 1A1, and 3A5.[34]

Studies have demonstrated 2 and 4 μg/kg dosing to be safe and effective for procedural sedation with no respiratory depression and minimal hypotension or bradycardia. Oral clonidine in the context of pediatric oral sedation is used commonly as a premedication that provides clinically relevant sedation and anxiolysis, analgesia, perioperative hemodynamic stability, and decreased opioid and anesthetic requirements.[35]

Dexmedetomidine

A relatively novel alpha-2 adrenergic agonist, dexmedetomidine, is used commonly in intensive care units and in pediatric procedural sedation as it provides varying degrees of anxiolysis, sedation, and analgesia.[23] Its affinity for alpha-2 over alpha-1 adrenergic receptors is 1620:1 and is 8 times more specific than clonidine.[24] The oral bioavailability of dexmedetomidine is 16% compared with parenteral routes being reported to be as high as 73% to 88%.[36] The elimination half-life is 2 to 3 hours.[23,24] Metabolism occurs via CYP2D6 hydroxylation and direct glucuronidation.[37]

Most recent investigations into sedation with dexmedetomidine include the parenteral routes, with IN and IV being most common. Because of the low bioavailability of oral dexmedetomidine, its efficacy may be limited for use in traditional oral formulations with regard to onset and duration of action.[38]

Research into utilization of dexmedetomidine for procedural sedation continues to show its safety and efficacy. Zub et al[39] demonstrated that 11 of 13 patients were able to successfully undergo procedures under procedural sedation or general anesthesia with preoperative administration of oral dexmedetomidine.[24] At the conclusion of their study, an oral dose for anxiolysis of 3 to 4 μg/kg was found to be ideal. A broad review conducted by Plambech and Afshari[31] found that among 51 pediatric studies, there were no reports of adverse events in relation to administration of oral dexmedetomidine for various procedures that included palatal repair surgery, pediatric cardiac catheterization, and lower abdominal surgeries.[23]

When used as a premedication for general anesthesia, there was no significant difference in separation anxiety from parents, acceptance of mask induction, or onset of delirium in dexmedetomidine compared with midazolam.[23] For invasive procedures such as cardiac catheterization, the addition of dexmedetomidine to other agents all used IV allowed for less movement during local anesthesia administration and throughout the procedure with a reduced need for airway intervention.[23] The combination of dexmedetomidine with other sedatives and anesthetics allows for the reduction of all agents administered, thus potentially reducing the risk of adverse events such as respiratory depression and agitation. An analgesic-sparing effect has also been demonstrated with dexmedetomidine administered in the postoperative period.

Although oral dexmedetomidine has less bioavailability than other parenteral routes, adjustments in dosing and timing can overcome these shortcomings in onset and duration. Zub et al[39] demonstrated remarkable efficacy of oral dexmedetomidine in a small cohort of pediatric patients with neurobehavioral problems. Dosing ranged from 1 to 4.2 μg/kg with observed success in placing an IV line in patients from 4 to 14 years of age.[39] Dexmedetomidine used either alone or in combination with oral and inhalational agents holds strong utility, with minimal effects on respiration compared with other traditional sedatives and anesthetic agents.

Tizanidine

Tizanidine is a centrally acting alpha-2 adrenergic agonist belonging to the imidazoline class. Like other alpha-2 adrenergic agonists, tizanidine inhibits presynaptic release of norepinephrine that decreases the postsynaptic release of the excitatory amino acids glutamate and aspartate from spinal interneurons.[26] Interneurons, also known as relay neurons, relay conduction from sensory neurons to motor neurons, and tizanidine presynaptically inhibits the action of the motor neurons.

Tizanidine is approved by the US FDA for management of muscular spasmodic conditions including multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, stroke, and traumatic brain injury.[40] Off-label uses include management of chronic neck and low-back pain, chronic migraines, refractory insomnia in spastic quadriplegic patients, and regional musculoskeletal pain syndromes.[26]

Tizanidine is commercially available as 2-, 4-, and 6-mg capsules and as 4-mg tablets with an oral bioavailability of 20% to 34%.[26] Oral bioavailability is increased to 80% when taken with food.[26] Drug metabolism occurs primarily via CYP1A2 isoenzymes, and its beta/elimination half-life is 2.5 hours with onset of action in about 60 minutes.[41] Miettinen et al[41] evaluated the sedative effects of tizanidine compared with clonidine in 6 healthy male individuals with doses of 4, 8, and 12 mg as compared with 150 μg of clonidine. In this case, 12 mg of tizanidine was comparable with 150 μg of clonidine.[27] Meanwhile Dadmehr's triple-blinded study found that the preoperative administration of

4 mg of tizanidine demonstrated a clinically significant reduction in pain scores for patients undergoing orthognathic surgery.[42] Tizanidine, while uncommonly used in traditional pediatric dentistry settings, may have limited utility in providing CNS depression in older pediatric patients with neurodiverse and special health care needs.

MISCELLANEOUS

Ketamine

Ketamine is a cyclohexanone derivative of phencyclidine, a nonbarbiturate dissociative anesthetic with an intended use for induction of general anesthesia and analgesia. It is a noncompetitive NMDA and glutamate receptor antagonist. It provides unique dissociative anesthesia along with agonism of opioid receptors. Properties include profound analgesia, intact pharyngeal-laryngeal reflexes, and cardiac and respiratory stimulation.[43] Its oral bioavailability is 16% and beta/elimination half-life is 45 minutes.[29] Drug metabolism occurs hepatically via N-dealkylation, hydroxylation, conjugation, and dehydration.

Special consideration should be taken while using this drug due to its emetogenic and sialagogic effects. In a review conducted by Oh et al,[44] ketamine administered alone or in combination with other meds was found to produce safe and effective sedation in pediatric populations with close and careful vital signs monitoring for dissociative anesthesia. In this review, the average dose found to produce adequate enteral sedation was 5 mg/kg; however, the potential for producing a level of sedation beyond minimal to moderate sedation was quite high with wide patient variability. Practitioner competency in being able to rescue a patient from a deeper than intended level of sedation along with airway compromise induced by ketamine's propensity to increase salivary secretions should be considered when using this sedative in oral regimens. In addition, some settings and regions may prohibit its use by personnel not trained in the administration and management of deep sedation or general anesthesia.

Zolpidem

Zolpidem is a short-acting "nonbenzodiazepine" hypnotic drug colloquially referred to as a member of the "Z-drug" family along with zopiclone and zaleplon. Binding still occurs on the $GABA_A$ receptor similarly to benzodiazepines; however, zolpidem demonstrates more specificity in subunit binding. Zolpidem decreases sleep latency and is primarily prescribed for the treatment of sleep-onset insomnia. Side effects of zolpidem mirror benzodiazepines and include drowsiness, headache, dizziness, and potential for respiratory depression. Metabolism occurs via CYP3A4 enzymes, and concentrations could be greatly increased if administered with CYP3A4 inhibitors like grapefruit juice or fluconazole.[45]

Zolpidem is administered orally and has a quick onset (~15 min) and 2- to 3-hour duration of action.[46] In a prospective randomized double-blind clinical trial conducted by Hanna et al,[46] 80 pediatric patients 2 to 9 years of age were given 0.5 mg/kg midazolam or 0.25 mg/kg zolpidem orally for presurgical premedication for anxiety.[32] The study demonstrated that zolpidem was similar to midazolam with regard to patient anxiety at the time of separation but inferior with regard to mask acceptance for general anesthesia induction. Typical adult dosing is 5 to 10 mg/dose with dosing dependent upon sex, most likely due to variations in CYP3A4 expression among males and females.

Melatonin

Endogenous melatonin is a naturally occurring hormone synthesized and released by the pineal gland. Melatonin is a major regulator of the sleep-wake cycle and circadian rhythms. A natural release of melatonin occurs during periods of environmental darkness and is suppressed by light with peak hours of release between the usual sleep period of 2 and 4 AM.[47] The anesthetic effect of melatonin is mediated through enhanced binding of GABA to its $GABA_A$ receptors.[48] Exogenous melatonin administration exerts a mild inducement of natural sleepiness but exhibits a reduced duration of sedation, accelerated recovery, and preservation of respiratory function unlike that of other orally administered CNS depressants. Side effects of exogenous melatonin administration include drowsiness, enuresis, headache, dizziness, diarrhea, and rash.[33] Metabolism is regulated by CYP1A2 and is inhibited by drugs such as fluvoxamine, which may produce higher serum concentrations than intended.[33]

Recently, melatonin has garnered some attention in the field of dentistry as a substitute for benzodiazepines as an oral sedative medication. Although limited evidence exists for the use of melatonin as an oral premedication in pediatric dental patients, some studies suggest that higher doses, such as 0.5 to 0.75 mg/kg, may yield greater efficacy.[3,34,49] Melatonin is available in 3- and 5-mg oral chewable tablets sometimes referred to as "gummies." Most melatonin regimens involve administration 30 to 60 minutes prior to the procedure. A systematic review encompassing 11 studies focused on preoperative pediatric patients revealed substantial variation in dosing, outcomes, outcome variables, and sample size.[35] However, in direct comparison to usual and

standard therapeutic doses of midazolam, melatonin sedation remains clinically ineffective for pediatric dentistry.[50]

CONCLUSION

Contemporary understanding of available medications and acceptable dosing for minimal and moderate enteral pediatric sedation is vital for achieving the highest patient safety outcomes possible. The most used drug classes in pediatric oral sedation include benzodiazepines, opioids, and antihistamines, with a more recent increase in the use of alpha-2 adrenergic agonists. Clearly, each drug class has its advantages and drawbacks, with practitioners considering and prioritizing therapeutic effects against risks and adverse effects. From the oral sedatives reviewed here, respiratory depression is the most likely serious adverse effect to be encountered when combinations of CNS depressants are administered in regimens that can potentiate the effects of singular medications.

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This continuing education (CE) program is designed for dentists who desire to advance their understanding of pain and anxiety control in clinical practice. After reading the designated article, the participant should be able to evaluate and use the information appropriately in providing patient care.

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CE questions must be completed within 3 monts and prior to the next issue.

1) Which of the following antihistamines with sedative properties is recommended to treat nausea and vomiting associated with pregnancy?

   a. Cetirizine
   b. Diphenhydramine
   c. Doxylamine
   d. Promethazine

2) Which of the following agents used in pediatric oral moderate sedation would be contraindicated for use in children with seizure disorder?

   a. Diphenhydramine
   b. Melatonin
   c. Meperidine
   d. Midazolam

3) Which of the following sedative medications is intended for use by practitioners trained to provide and monitor pediatric patients at a level of deep sedation and general anesthesia?

   a. Chloral hydrate
   b. Diphenhydramine
   c. Hydroxyzine
   d. Ketamine

4) Which of the following sedative medications provides a possible extended duration of action due to enterohepatic circulation of active metabolites?

   a. Clonidine
   b. Dexmedetomidine
   c. Diazepam
   d. Zolpidem