THE DENTAL CLINICS OF NORTH AMERICA

Dent Clin N Am 46 (2002) 781–802

Inhalational and enteral conscious sedation for the adult dental patient

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N_2O/O_2 inhalational sedation and enteral sedation are inherently well suited for inducing a level of central nervous system (CNS) depression that is consistent with conscious sedation for a broad population of dental patients. With the appropriate patient population and sufficient training and office preparedness, these two sedation techniques are safe and effective. As discussed elsewhere in this issue, the amount of training necessary to deliver these forms of conscious sedation is considerably less than that required to provide parenteral sedation and general anesthesia. Additionally, both of these forms of sedation have a high level of patient acceptance because the general population perceives minimal discomfort and inconvenience with these techniques. Given the unpleasant nature of many dental procedures, the use of these forms of sedation can make these dental treatment experiences more pleasant for the patient and the dental care providers.

Nitrous oxide is the only inhalational agent that is practical for producing conscious sedation. In contrast to only one inhalational sedative, many enteral sedatives are available, with many having applications in the dental treatment setting. The goal of this article is to comprehensively review N_2O/O_2 inhalational sedation and enteral sedation in the context of conscious sedation for adult dental patients. The pharmacologic properties of nitrous oxide and several oral sedatives are reviewed in this article. Additionally, the techniques of inducing sedation with these pharmacologic agents and monitoring the physiologic status of sedated patients are also discussed. The

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PII: S0011-8532(02)00029-0

adaptation of these sedation techniques for the pediatric population of dental patients is covered in another article.

Nitrous oxide/oxygen inhalational sedation

The historical use of nitrous oxide as a clinical anesthetic is founded in the pioneering work of two dentists, Horace Wells and William T.G. Morton. Nitrous oxide remains one of dentistry's most valuable sedatives. Many physical and clinical properties account for the success of nitrous oxide as an inhalational sedative. The coadministration of nitrous oxide and oxygen results in a sedative technique that is safe and highly efficacious in a large population of mildly apprehensive dental patients. Besides producing sedation, nitrous oxide also produces analgesia and mild skeletal muscle relaxation. Although the exact mechanism of action for nitrous oxide's sedative and analgesic properties has been elusive, the CNS activation of opioid-dependent pathways [1], benzodiazepine receptors [2], and the inhibition of excitatory amino acid receptors [3] are among the likely candidates.

Physical properties, pharmacokinetics, and pharmacodynamics

At room temperature and one atmospheric pressure, nitrous oxide is a colorless nonflammable gas. Even though nitrous oxide is nonflammable, it supports combustion [4]. Nitrous oxide has a mild odor and taste that is described as pleasant by most patients. Additionally, this gas is not irritating to the mucosa of the respiratory system. Nitrous oxide is supplied as a liquid in equilibrium with its gas phase (the gaseous portion located above the liquid) in pressurized metal cylinders. The pressure of the equilibrated gas above the liquid in the cylinder is approximately 750 psi. Dispensing any of the gaseous contents from the cylinder results in a rapid vaporization of some of the remaining liquid to replace the lost gas and restore equilibrium. This action continues until there is no more nitrous oxide liquid in the cylinder to vaporize. Therefore, the gas pressure at the top of the cylinder remains at 750 psi until almost all of the liquid vaporizes. Once the liquid form is depleted there is a quick decline in gas pressure and a rapid depletion of the remaining gas in the cylinder. This property of nitrous oxide makes it difficult to determine with great accuracy how much gas remains in a pressurized cylinder. The most accurate (but inconvenient and impractical) way to determine how much nitrous oxide remains is by intermittently weighing each cylinder while it is in service.

Oxygen is always coadministered with nitrous oxide at a minimum concentration of 30% (the importance of coadministering oxygen with nitrous oxide and the accompanying safety considerations are discussed in greater detail a little later). Oxygen is also supplied in pressurized cylinders, having a pressure of approximately 2000 psi when full. In contrast to nitrous oxide,

the oxygen in pressurized cylinders is only in the gaseous state. Therefore, the pressure displayed on the gas regulator is an accurate reflection of the amount of gas remaining in the cylinder (ie, 1000 psi means that half of the total gas supply remains).

The CNS depression that results in sedation depends on the concentration of the sedative in specific brain regions and how these concentrations change as the sedative agent attempts to achieve a state of equilibrium with other bodily tissues (eg, muscle, adipose stores). These same properties of sedation apply to the inhalation of nitrous oxide. Nitrous oxide is poorly soluble in blood. Being poorly soluble in blood results in a small percentage of nitrous oxide being removed from the inhaled mixture of gases in the lung's alveoli before a state of equilibrium is reached between the concentration of gas in the arterial blood supply and air in the alveoli. This property of nitrous oxide results in a rapid onset of sedation (induction) and a quick resolution of the sedative effects (emergence) when the gas is turned off.

A key factor that accounts for nitrous oxide's safety in the practice of dentistry is that it is not a potent anesthetic gas. The minimum alveolar concentration (MAC) is a convenient measure for comparing the potency of anesthetic gases. MAC is defined as the alveolar concentration of an anesthetic at which 50% of patients fail to respond to a standard surgical stimulus [5]. The MAC for nitrous oxide is approximately 105%. Because the nitrous oxide concentrations for producing sedation and analgesia in dental settings are typically in the range of 20–50%, reaching a state of CNS depression in which patients are nonresponsive is highly unlikely without the use of a hyperbaric chamber.

The poor solubility of nitrous oxide in blood and its mild potency are two of the characteristics that make N_2O/O_2 sedation well suited for conscious sedation in dentistry. The characteristics of nitrous oxide are ideally suited for titrating within a wide concentration range the amount of this inhaled sedative necessary to achieve a specific level of CNS depression. By communicating with the patient about the clinical signs of sedation they may or may not be experiencing, adjustments in the inhaled concentration can be made during the dental procedure as needed. This allows for changes in the level of sedation as needed (eg, deeper levels of sedation during the injection of local anesthesia versus lighter levels of sedation during the application of fluoride). The poor solubility of nitrous oxide in blood also means that the latency to observe the desired change in CNS depression after manipulating the inhaled concentration of the gas is short.

Because oxygen concentrations of at least 30% are always coadministered with nitrous oxide, adverse events related to hypoxia and tissue ischemia are not likely with this sedation technique. The cardiovascular and respiratory systems are minimally affected by N_2O/O_2 sedation. Nitrous oxide usually produces no clinically significant changes in cardiovascular function. It has weak myocardial depressant effects and mild sympathomimetic effects [6]. The result of these two opposing effects is usually no clinically evident net

change in cardiovascular function. Similarly, nitrous oxide has minimal effects on respiratory function. Although nitrous oxide decreases tidal volume slightly, it also increases respiratory rate, producing a minimal net change in normal patients. Patients whose respiratory drive comes from low oxygen tensions in blood (eg, chronic obstructive pulmonary disease, emphysema), however, represent relative contraindication to N_2O/O_2 sedation. It is the concomitant administration of oxygen, not the nitrous oxide, which produces the problem in these patients. The administration of oxygen concentrations in excess of 30% may be sufficient to blunt the respiratory drive that is driven by hypoxia in these patients [7].

Administration technique and recovery

The induction of anesthesia with nitrous oxide is not technically difficult. An inspection of the system that delivers the gases is an important first step before sedating the patient. Making sure all of the necessary equipment is present and in working order facilitates a smooth induction by eliminating unnecessary technical distractions in the presence of the patient. Most importantly, this inspection should include making sure that an adequate supply of oxygen and nitrous oxide is available, that there are no gas leaks in the system, and that the scavenging system is working properly.

Although not suggested in the sedation guidelines in many states, measuring and recording baseline vital signs is highly recommended immediately before administering any sedative agent to a dental patient. This should include blood pressure, heart rate, and respiratory rate. After verifying that the baseline vital signs are within normal limits and that the consent for the anesthetic and the dental procedure has been obtained, it is time to begin the sedation procedure. Administering oxygen at a concentration of 100% is always the initial part of the induction. A total flow rate of 5–7 liters of gas per minute is typical for the average adult. Adequacy of the chosen flow rate can be determined by observing the reservoir bag on the machine delivering gas. If the bag is completely collapsed the gas flow rate needs to be increased. Conversely, if the bag is completely distended the gas flow rate needs to be decreased.

After establishing that the total gas flow rate is adequate and that the patient is comfortable, the titration of nitrous oxide should commence. Recognizing that there is a great deal of inter- and intrapatient variability in the concentration of nitrous oxide that produces sedation, initial titration at approximately 20% nitrous oxide is a prudent starting point. The rate of sedation induction with nitrous oxide depends on the concentration and the rate and depth of respiration. Instructing the patient to inhale and exhale exclusively through their nose at their regular respiratory rate and depth helps speed the induction. Because titration to the desired effect is one of the benefits of this inhalational technique, make sure that the patient is aware of the signs that the gas produces at concentrations relevant to sedation.

Among the signs and sensations of N_2O/O_2 sedation are feelings of relaxation, tingling in the extremities, circumoral numbness, floating or sinking sensations, changes in the perception of auditory stimuli, and bodily warmth. Titration of increasing concentration of nitrous oxide should continue until the patient is comfortable and experiences any set of these signs.

The delivery of dental treatment should begin once the patient reaches a comfortable level of sedation. By titrating the concentration of nitrous oxide, a higher percentage can be administered during more stressful portions of the procedure (50–70%), producing more profound sedation. In contrast, the concentration of nitrous oxide can be reduced to a lower concentration when the level of stress or stimulation is lower (20–40%). The dentist delivering N_2O/O_2 sedation needs to be attentive to the patient and the sensations they are experiencing, because certain symptoms indicate that nitrous oxide concentrations are too great. Among these symptoms are dysphoria, uncontrolled laughter, sweating, nausea, marked lethargy, unresponsiveness, and the inability to follow commands. The concentration of nitrous oxide should be either immediately decreased or discontinued if these symptoms are encountered.

On completion of the dental procedure or the portion of treatment for which N_2O/O_2 sedation was indicated, the flow of nitrous oxide is discontinued and 100% oxygen is delivered at the predetermined gas flow rate for 3–5 minutes. The poor solubility of nitrous oxide in blood also accounts for the rapid resolution of the signs and sensations of nitrous oxide sedation. Within the 3–5 minutes that the patient is breathing 100% oxygen, the signs and sensations of nitrous oxide sedation usually disappear. Engaging the patient in conversation is a good way for assessing their return to baseline.

The practice of delivering 100% oxygen for 3–5 minutes after nitrous oxide is discontinued has been advocated to prevent diffusion hypoxia. Diffusion hypoxia was first described in 1955 [8]. The poor solubility of nitrous oxide that facilitates a rapid induction also facilitates a rapid dissipation of the effect and removal of the gas from the bloodstream once the gas supply is decreased or discontinued. Because the excretion of nitrous oxide is greater than the uptake of nitrogen from room air in the alveoli, a dilution of alveolar oxygen can occur, resulting in hypoxia. The results of clinical studies measuring end-tidal oxygen concentrations and hemoglobin saturation by way of pulse oximetry in normal, healthy patients with normal respiratory rates, however, do not support this hypothesis because hypoxic conditions during recovery were not evident [9–11]. Although brief reductions in oxygen concentrations and hemoglobin saturations occur immediately after discontinuing nitrous oxide administration, levels indicating hypoxia are not evident, especially in populations of dental patients being treated with no other systemic medications. Collectively, these results suggest that diffusion hypoxia is not a significant problem in the dental setting. Even though diffusion hypoxia is not a concern in most dental patients who have received N_2O/O_2 sedation, it remains prudent to administer 100% oxygen to facilitate an uneventful recovery.

Although not suggested in most sedation guidelines, it is also prudent to measure and record the patient's vital signs once the recovery is complete and the patient is about to be dismissed. Unlike any of the other sedation techniques in which a pharmacologic agent is administered, an adult escort is not necessary at the completion of the procedure. Documentation that supports your assessment of the patient's return to baseline and the resolution of sedative effects is important because the patient can be released without an escort after treatment.

On rare occasions one may encounter a patient who requires more than the usual 3–5 minutes to have the signs and sensation of the inhalational sedation disappear. Although this can be disconcerting to the patient and the dentist, continuing to administer 100% oxygen to the patient, monitoring their vital signs, and reassuring them that this is a normal response in some patients is important. This should be continued until the patient recovers sufficiently to be dismissed from the office.

Safety precautions

Besides striving to effectively relieve patient fear, the dentist providing N_2O/O_2 sedation must also make sure that it is delivered safely. The systematic use of a risk management plan that assesses the patient's physical and psychologic health, as described earlier, is only one part of the process that increases the safety of this sedation technique. The analgesia machine that delivers the nitrous oxide and oxygen incorporates several safety features also. The most important of these safety features are the "fail safe" mechanism and color-coding and pin indexing of the compressed gas supply.

The most important safety feature of the analgesia machine ensures that the patient does not become hypoxic secondary to receiving a mixture of gases that does not contain enough oxygen. This "fail safe" mechanism never allows the delivery of nitrous oxide unless there is oxygen flowing through the machine. For example, if the compressed gas cylinder containing oxygen becomes empty during the procedure, the machine automatically shuts off and delivers no nitrous oxide. Similarly, if the dentist forgets to open the compressed gas cylinder containing oxygen, no nitrous oxide flows through the system for delivery to the patient.

Because the metal cylinders that contain compressed gas all look similar, additional safety mechanisms are in place. A couple of methods are used to distinguish the contents of the cylinders, making it unlikely to mistakenly connect a nitrous oxide cylinder to the oxygen portal of the analgesia machine. The simplest method involves the assignment of different colors to the cylinders depending on the gas they contain. All oxygen cylinders in the United States are green, and nitrous oxide cylinders are blue. If practicing outside of the United States, however, one should be aware that this color-coding system is not universal (eg, oxygen cylinders are white in Canada).

An additional method for preventing the inadvertent attachment of cylinders containing nitrous oxide to the oxygen portal of portable analgesia machines is the system of pin indexing. Two small holes have been drilled into the valve stem of each gas cylinder. These two small holes correspond to the location of two small pins that extend slightly from the section of the analgesia machine's yoke where the compressed gas cylinders connect. These pins of the machine fit snugly inside the holes of the cylinder. The location of the two pins (and the corresponding holes in the cylinder's valve stem) is different for each gas, making it impossible for the incorrect cylinder to be attached to the yoke. A modification of the pin index system has been developed for cylinders of compressed gas that are larger than the portable ''E'' size (centrally plumbed facilities). The thread size of the connectors for the larger cylinders (''D'' and ''G'' sizes) is unique for each gas, making the inadvertent connection of nitrous oxide to oxygen receptacles impossible.

Even though the analgesia machine has several built-in safety features, the diligence of the operator is still the most important factor in assuring that nitrous oxide administration is safe. The most serious of reported complications involves inadvertent hypoxia and death as a result of plumbing mishaps involving reversal of the gas sources to the apparatus [12]. Dislodging of the pins from the pin index connector of portable units and crossing the connections of oxygen and nitrous oxide lines in facilities with central gas plumbing are the most likely causes of these types of mishaps.

Health hazards associated with nitrous oxide and their prevention

Although nitrous oxide is not acutely toxic, several reports have alerted healthcare professionals that there are significant risks associated with chronic exposure to nitrous oxide. Operating room personnel (eg, anesthesiologists, operating room nurses) and dentists seem to be at the greatest risk for chronic exposure because of the frequency that this anesthetic gas is used in their working environments. Because nitrous oxide is the fifth most common inhalant used for recreational purposes in the United States, adolescents are also at risk for the manifestations of toxicity secondary to chronic exposure [13].

The health hazards that have been indicated with acute and chronic nitrous oxide in the dental office have been extensively explored [14]. The health hazards most frequently associated with nitrous oxide are the production of adverse neurologic symptoms, impaired reproductive capability, and teratogenicity. The neurologic symptoms resemble those caused by a vitamin B12 deficiency. These symptoms include paresthesias, diminished proprioception and vibration sensation, cutaneous sensation, motor weakness, clonus or hyperreflexia, areflexia, autonomic dysfunction, gait disturbance, intellectual or behavioral impairment, and impaired visual acuity [15]. The mechanism through which chronic nitrous oxide exposure produces these symptoms is the irreversible oxidation of the cobalt ion of

cyanocobalamin, thus preventing it from acting as a coenzyme in the production of methionine [14,16]. Clearly, many of these neurologic symptoms are not conducive to the practice of dentistry, so all members of the dental staff need to be aware of these risks and take appropriate measures to prevent inadvertent and intentional (recreational) chronic exposure.

The relationship between nitrous oxide exposure in the workplace and reproductive health is among the most frequently studied topics in reproductive epidemiology. Despite this attention, no clear consensus exists about the risk for outcomes like spontaneous abortion in humans [17]. It is clear that nitrous oxide exposure in laboratory animals causes malformations and decreases live litter size. The results of epidemiologic research suggest that exposure to unscavenged nitrous oxide for as little as 5 hours per week is associated with reduced fertility in women [18]. Similarly, unscavenged nitrous oxide also increases the risk for spontaneous abortion [17]. These are difficult studies to perform and analyze because of the possibility of selection bias in identifying the study population and recall bias among the participants. Additionally, improvements in the scavenging of nitrous oxide in dental offices make it difficult to compare the results of older studies with those conducted more recently. Despite these difficulties and possible limitations, it is prudent to have an effective scavenging method to protect the reproductive health of women in the office who are of reproductive age. Additionally, pregnant patients should not be administered nitrous oxide, and any pregnant office staff should not work directly with patients who are receiving nitrous oxide.

Active scavenging of nitrous oxide in the dental environment is the most effective way for minimizing one's chronic exposure to nitrous oxide. Current guidelines from the National Institute for Occupational Safety and Health (NIOSH) recommend that the time-weighted exposure to nitrous oxide not exceed 25 ppm for any healthcare worker. Because closed systems with endotracheal tubes are used when administering anesthetic gases to patients in the operating room environment, scavenging nitrous oxide and other gases is fairly easy, leading to minimal pollution of the workplace with traces of these gases. The dental operatory, however, offers a unique set of challenges for keeping the exposure at less than 25 ppm. For starters, the "open" system for administering the gas offers plenty of opportunities for gases to escape into the operatory. A good fit of the mask over the patient's nose is critical. The total gas flow also should not be excessive. Excessive gas flow through the system (as indicated by a fully inflated/distended reservoir bag) facilitates leaking of gas between the mask and the patient's face. Patients who talk a lot during nitrous oxide administration also contribute to pollution of the operatory. The scavenging mechanism for many analgesia machines occurs exclusively at the nosepiece, removing most of the nitrous oxide during patient exhalation. Talking and mouth breathing result in a fair amount of gas being exhaled through the mouth into the open air. The analgesia machine connections and its tubing also should be regularly inspected for leaks.

Enteral sedation with a single agent

Similar to N_2O/O_2 sedation, oral sedatives also have a place in the practice of dentistry. Several characteristics of the enteral route of administration make this route of administration for sedatives well suited for dentistry. Perhaps the most favorable characteristic of this administration route is the ease of administering the agents to most adult populations. Oral drug administration is not technically difficult and does not require special instrumentation to deliver the sedatives. Equally important is the high level of patient acceptance to receiving sedatives by mouth, compared with more invasive techniques required for parenteral sedative administration.

Despite the many favorable characteristics of enteral sedation, there are a few disadvantages that are inherent with this method. The prolonged latency to the onset of sedative effects introduces some inconvenience that can be overcome with adequate consideration given to the timing of drug administration. The most problematic aspect of the disadvantages, however, is the inability to titrate the drug administration to a desired endpoint of sedation. Accordingly, careful consideration needs to be given to determining the appropriate dose for each patient situation. There is also a great deal of inter- and intrapatient variability in the response to oral sedatives, adding to the unpredictability of the sedative effect. Variability in drug absorption across the gastrointestinal mucosa and the hepatic first-pass effect are among the factors that lead to the unpredictable nature of this mode of sedation. In the most serious of situations, a relative overdose of the sedative may be given, resulting in too much CNS depression, the loss of consciousness, and the ability of the patient to maintain their protective reflexes (eg, patent airway). At the other end of the variability spectrum is the relative underdosing of the patient. An apparent lack of efficacy occurs in these situations, leading to patient and dentist dissatisfaction. Patient recovery after enteral sedation presents another disadvantage. Unlike N_2O/O_2 sedation, the patient must have a responsible adult escort to take them home at the end of the procedure because of lingering blood concentrations of the drug that impair judgment.

Most states permit dentists to prescribe and administer single enteral agents (either alone or in combination with N_2O/O_2) without additional training or credentialing beyond their undergraduate dental school curriculum. If a dentist wishes to administer multiple enteral sedatives concomitantly, however, additional training and certification is necessary. This discussion focuses on the delivery of single sedative agents, either by oral ingestion or absorption across intraoral mucosa (transmucosal absorption). The following discusses the attributes and disadvantages of producing sedation in adults with the benzodiazepines, an imidazopyridine, antihistamines, and barbiturates. A discussion of the use of chloral hydrate for producing sedation can be found elsewhere in this issue.

Benzodiazepines

Perhaps the most used and safest group of sedative drugs found in dentistry are the benzodiazepines. To fully appreciate the many pharmacologic properties of the benzodiazepine drug class, a brief review of the gamma-aminobutyric acid (GABA) system of neurotransmission is necessary. GABA is one of the primary inhibitory neurotransmitters within the CNS. GABA is the ligand for a heterogenous group of membrane-bound receptors ($GABA_A$) found in several CNS regions. Activation of GABA-dependent pathways within the CNS results in many effects that may be beneficial to capitalize on in the dental setting. These beneficial effects of GABA-mediated neurotransmission include anxiolysis, muscle relaxation, and generalized CNS depression. Of particular importance is the $GABA_A$ receptor activation of cerebral cortex regions that formulate emotional responses, such as the limbic system. $GABA_A$ receptors are associated with opening chloride ion channels on postsynaptic neurons. The net result is an increase in the conductance of chloride ions to the intracellular space of neurons (hyperpolarization), and the accompanying increase in stimulus strength needed to activate the affected postsynaptic neurons.

There are many different benzodiazepines, each having its own subtle pharmacologic difference. In general, the benzodiazepine drug class has a wide margin of safety, making them ideal for many dental applications. This wide margin of safety for benzodiazepines is because of their indirect mechanism that increases GABA-mediated effects. Rather than binding directly to the $GABA_A$ receptor-binding site, benzodiazepines bind to the omega receptor (formerly known as the ''benzodiazepine receptor'') of the $GABA_A$ receptor complex [19]. Benzodiazepine binding to the omega receptor increases the binding affinity of GABA for its binding site on the $GABA_A$ receptor complex, resulting in an increased frequency in opening of its associated chloride channel [20]. This increase in intracellular chloride ions produces a state of neuronal hyperpolarization and the apparent inhibition of the postsynaptic neuron with the usual amount of synaptic activity.

The benzodiazepines have a wide variety of uses. They have selective anti-anxiety properties, some somnolence, strong anticonvulsant properties, and centrally mediated muscle relaxation. Some of the benzodiazepines also produce mild to profound anterograde amnesia. The effects the dentist wishes the patient to experience greatly influence which benzodiazepine to dispense. Table 1 compares the benzodiazepines commonly used dentistry.

A significant part of the decision-making process when selecting a benzodiazepine for conscious sedation should include the drug's pharmacokinetic properties (ie, getting the drug to and from the receptor) and its pharmacodynamic properties (ie, the drug effect occurring at the receptor). Once in the bloodstream, most of the benzodiazepines are heavily bound to plasma proteins such as albumin, resulting in less than 5% of the ingested dose being free to bind to the receptor and exert an effect. This means that in patients

Table 1
Enteral sedatives used for conscious sedation in dentistry that bind to the omega (benzodiazepine) receptor

Omega receptor agonist	Suggested adult enteral dose	Estimated working time	Miscellaneous
Diazepam (Valium®)	5–15 mg	1–2 h	Prototypic benzodiazepine Needs to be taken 1 h before appointment Active metabolites that can produce sedation for 2–3 days Excellent muscle relaxant Not recommended for elderly patients or those with impaired liver function
Triazolam (Halcion®)	0.25–0.5 mg	1 h	Rapid onset Needs to be taken 30–45 min before appointment Excellent anxiolytic Frequently produces amnesia Works well with N_2O/O_2
Midazolam (Versed®)	0.5 mg/kg	1 h	Rapid onset Excellent anxiolytic Frequently produces amnesia Available as an oral suspension (2 mg/ml) Works well with N_2O/O_2 Expensive
Alprazolam (Xanax®)	0.5–1 mg	1–2 h	Needs to be taken 1 h before appointment Excellent anxiolytic
Lorazepam (Ativan®)	1–2 mg	2–3 h	Needs to be taken 1–2 h before appointment Excellent anxiolytic
Zolpidem (Ambien®)	10 mg	1 h	Imidazopyridine drug class, NOT a benzodiazepine Rapid onset Needs to be taken 20–30 min before appointment Excellent anxiolytic Works well with N_2O/O_2
Receptor antagonist			
Flumazenil (Romazicon®)	0.2–1.0 mg	1 h	Best if given IV Acceptable absorption when given sublingual or IM[a] Dose should be increased if given Sublingual or IM[a] Because of the possibility of rebound sedation, the patient must be monitored for 60–75 min after antagonist administration

[a] *From* Heniff MS, Moore GP, Trout A, et al. Comparison of routes of flumazenil administration to reverse midazolam-induced respiratory depression in a canine model. Acad Emerg Med 1997;4:1115–8.

with reduced plasma protein (elderly patients, abusers of ethanol, patients suffering from malnutrition resulting in emaciation, and patients with severe liver disease), the benzodiazepine dose needed to achieve the desired effect may be considerably less than normal. As discussed later, the various benzodiazepines have distinct pharmacokinetic "personalities" that dictate their onset and duration of action profiles. The dentist should consider these "personality profiles" when selecting a benzodiazepine for a particular patient and procedure.

Another consideration when using benzodiazepines for conscious sedation is that many of them undergo oxidative metabolism by way of the hepatic cytochrome P450 enzymes. As a result, other medications the patient may be taking might significantly alter the amount of benzodiazepine that is available by either delaying the metabolism of the benzodiazepine or accelerating it. Thus, the dentist prescribing benzodiazepines should always refer to cytochrome P450 drug interaction tables when making decisions about administering benzodiazepines.

The adverse effect profile of benzodiazepines is minimal. Excessive CNS depression and respiratory depression occur in overdose situations. Excessive CNS depression is usually manifest as severe alterations in consciousness, ranging from weak or inappropriate responses to verbal commands or stimulation to the loss of consciousness. Depression of respiration (eg, patency of the airway, rate or depth of breathing) that requires intervention is an indication that an overdose has occurred. Careful dosing of the benzodiazepines decreases the likelihood of these adverse effects, but additive or supra-additive CNS depression is a reality with other drugs that produce CNS depression (ethanol, opioids, antidepressants). In situations in which a benzodiazepine is likely to contribute to severe respiratory depression and the inadequate oxygenation of the patient, the benzodiazepine receptor antagonist flumazenil may need to be administered in conjunction with positive pressure ventilation. Flumazenil needs to be readily available when using benzodiazepines to produce sedation (for review, see articles by Jackson and Johnson, and Haas in this issue). An interesting and not wholly unusual adverse reaction is simply paradoxic in nature. Instead of becoming more sedate and relaxed, affected patients become more agitated or fearful than they were before dosing with the benzodiazepine.

Benzodiazepines exhibit weak dependence liability, but addiction can occur with their prolonged use (addictions to benzodiazepines are among the most difficult to break). This class of sedative should be used with caution in patients with hepatic or renal disease because of obvious metabolism and excretion concerns, respectively. Similarly, caution is necessary when considering benzodiazepine sedation for patients with narrow-angle glaucoma because of their mild anticholinergic properties. All of these conditions should alert the dentist to the need for a consultation with the patient's physician. Given the high teratogenesis potential, benzodiazepines are not to be used with women who are or might be pregnant.

Diazepam (Valium®)

Perhaps the most familiar sedative agent in dentistry, diazepam has a long and successful record in helping relieve mild to moderate dental procedure-evoked anxiety. The "personality" of diazepam includes strong antianxiety effects but minimal somnolence and virtually no amnesia at orally prescribed doses. Diazepam is lipid soluble, which is important in the sedative's onset. Diazepam has long-acting metabolites (oxazepam and desmethyldiazepam), however, that have sedative properties. Consequently, the clinical duration of diazepam sedation tends to be moderate to long in length. Diazepam readily redistributes into lipid structures, and a clinical "rebound" effect can occur when this sequestered drug is re-released into the bloodstream after a meal. It is not uncommon for patients who have been sedated earlier to get drowsy after eating, so they should be warned of this possibility. Diazepam is supplied in 5- and 10-mg tablets. The typical adult dose is 5–10 mg daily (PO) 1 hour before the procedure. If patient sedation with this dose range is not successful (eg, patient experiences minimal signs of sedation), the dose can be cautiously increased to a total of 15–20 mg for subsequent sedations, paying close attention for the onset of unwanted side effects (eg, unresponsive to verbal commands). Diazepam is classified as Pregnancy Risk Category D. It is a substrate of the cytochrome P450 isozymes 2C19 and 3A4, so medications that activate or retard the activity of those isozymes affect the metabolism of diazepam.

Diazepam is an ideal medication for patients who are a bit anxious about the procedure and want "the edge taken off." It does not cause significant somnolence or amnesia, and is a poor choice when those are the desired effects. Another indication for diazepam is the patient who has been successfully sedated with it in the past and has great personal confidence in its ability to provide sedation for future treatments. Patients, especially the elderly and physically debilitated, should be warned that residual sedative effects are likely for the few days after the procedure. Accordingly, patients should exercise caution in making important decisions and may wish to refrain from driving and operating machinery during this period.

Triazolam (Halcion®)

Triazolam is one of the more potent benzodiazepines. It has a short half-life because it is rapidly redistributed and rapidly metabolized. Similar to the other benzodiazepines, triazolam is a full agonist at the omega receptor and potentiates the CNS depression produced by other sedatives. Triazolam's personality is one of rapid onset, short duration of action, and profound anterograde amnesia. Originally developed as a medication for treating insomnia, it has the ability to induce a somnolent state. Unfortunately, the suggested dose of triazolam for treating insomnia was too high when the drug was first introduced to the market, and the importance of medical supervision was not emphasized adequately [21]. Consequently, the early

occurrence of unwanted side effects prompted many to question triazolam's safety. Careful review of the problems resulted in many changes in the way triazolam was prescribed, and the drug's safety is no longer in question.

The combination of probable amnesia and somnolence has brought triazolam into the forefront as a preferred sedative among dentists who use oral sedation in their practices [22,23]. Triazolam is supplied in 125 μg (0.125 mg) and 250 μg (0.25 mg) tablets. The typical adult dose is 250–375 μg PO or sublingual 30–45 minutes before the procedure. Clinical research suggests that the sublingual route for triazolam administration may be slightly more efficacious secondary to slightly higher plasma concentrations compared with the oral route [24]. Triazolam carries a Pregnancy Risk Category X, and must not be used if there is any possibility the patient might be pregnant. It is metabolized by the cytochrome P450 enzyme system.

Triazolam is well suited for the average dental appointment that lasts no more than 1 hour. The patient can come to the office early, take the sedative in the waiting room, and be comfortably sedate for their appointment within 30–45 minutes. Most appealing for this benzodiazepine is its profound amnesia. Patients have little or no recall the following day of details associated with their appointment. If coadministered with N_2O/O_2 inhalational sedation, the sedative effects can be as profound as a combined benzodiazepine/opioid intravenous sedation.

Some dentists have recently started to administer additional sublingual doses of triazolam when the clinical effects begin to wane and they want to perform additional dentistry during the appointment. There are little or no data to support the safety of this practice, and there is growing concern that many of these patients may become profoundly sedate, perhaps even losing consciousness, with more than one sedative administration within such a short window of time. Also, although many state laws allow "single oral agent" sedation, those laws were written with the intent that the "single agent" would be given as a "single dose." Although the practice of oral re-dosing may seem reasonable to those with a naive background in pharmacology, we urge dentists *not* to adopt this practice until scientific and legal issues regarding the method can be sorted out. Given the numerous scientific questions that remain with this practice, dentists choosing to adopt the technique of oral re-dosing with triazolam or any other oral sedative should obtain the additional training necessary to administer deeper levels of sedation and obtain a permit through their region's quality assurance division (eg, state licensing bureau). Additionally, we strongly recommend that physiologic monitoring be used and recorded at least every 15 minutes (preferably every 5 minutes during the procedure). This should most importantly include monitoring of airway patency and respiratory function (by way of a precordial/pretracheal stethoscope), tissue oxygenation (by way of pulse oximetry), blood pressure, and heart rate. This degree of monitoring is necessary when using sedation techniques with a greater risk for rendering the patient unconscious. Although probably not intentional, the practice of re-dosing falls into this category of risk.

Midazolam (Versed®)

Midazolam has been a popular benzodiazepine for parenteral sedation in dentistry since the mid 1980s. Midazolam has recently been gathering favor as an oral/transmucosal sedative also. Midazolam is known to have a marked first-pass effect in the liver, making the transmucosal route slightly preferable for achieving sedation. This can be either from nasal inhalation, rectal administration, or PO (with emphasis on maximizing the time spent retaining the solution in the mouth before swallowing). The typical dose is 0.25–0.5 mg/kg PO, maximum 20 mg 20–30 minutes before a procedure. Midazolam is supplied as an elixir (2 mg/mL) exclusively for oral administration, or as a 5-mg/mL solution (formulated for injection) that can be combined with a vehicle such as nonparticulate fruit juice or sugary powder (eg, Kool-Aid®) to make a reasonably palatable mixture. The drug is highly distasteful without some sort of alteration.

Because midazolam is expensive compared with other orally administered sedatives, often it is not cost effective to use in the adult population. Most of the oral/transmucosal administration of midazolam for dental sedation takes place in the pediatric dental environment. Although effective in the adult patient, midazolam by way of the enteral route is best for short procedures. The medication is classified as Pregnancy Risk Category D, and is a substrate for the CYP 3A4 isozyme. It has a personality similar to triazolam in that it can induce profound amnesia, moderate somnolence, and is short acting.

Lorazepam (Ativan®)

Lorazepam is one of the more hydrophilic benzodiazepines that are available for PO administration. The hydrophilic property of lorazepam makes it more difficult for this benzodiazepine to cross the blood–brain barrier. As a result, lorazepam has a longer time to the onset of sedation and requires a long time for recovery. Like diazepam, lorazepam has minimal somnolent and amnesic effects, giving a clinical profile of a long-acting anxiolytic agent. Unlike diazepam, it has no active metabolites, and is therefore devoid of rebound effects during the time surrounding the recovery. Lorazepam is supplied in 0.5-, 1-, and 2-mg tablets. The typical adult dose is 1–2 mg PO, 1–2 hours before the procedure. Lorazepam is also a Pregnancy Risk Category D drug. Lorazepam is not metabolized by the cytochrome P450 enzyme system.

Lorazepam is best suited for sedating the anxious patient who is undergoing long dental procedures (2–3 hours). Lorazepam is also a good sleep aid, taken at bedtime the night before the appointment, to help the anxious patient get a good night's sleep and be well rested before their appointment.

Alprazolam (Xanax®)

Alprazolam has the nice characteristic of having a half-life longer than triazolam but shorter than lorazepam. Alprazolam is almost a pure

anxiolytic drug; it produces little or no amnesia or somnolence. It is supplied as 0.25-, 0.5-, 1-, and 2-mg tablets. The typical adult dose is 0.5–1 mg 1 hour before the procedure. It is classified as Pregnancy Risk Category D, and is a substrate of the CYP 3A4 isozyme. Recommendations for the use of alprazolam include when anxiolysis without somnolence is the major goal, and the dental appointment will be 1–2 hours in length.

Imidazopyridines

A novel addition to the sedative market is zolpidem (Ambien®). Zolpidem, a member of the imidazopyridine drug class, is distinct and unrelated to the benzodiazepines. Zolpidem binds to and stimulates a benzodiazepine omega receptor of the $GABA_A$ receptor complex, however. Similar to the benzodiazepines, zolpidem binding to the omega receptor increases the binding affinity of GABA for its binding site on the $GABA_A$ receptor complex, resulting in neuronal hyperpolarization and the apparent inhibition of the postsynaptic neuron with the usual amount of synaptic activity. Its clinical sedation actions therefore mimic those of the benzodiazepine family of sedatives (see Table 1). Classified as a hypnotic, one of zolpidem's most remarkable clinical attributes is its rapid onset and short duration of action. Clinically evident sedation is typically produced in approximately 20 minutes. Zolpidem's personality is such that it provides anxiety relief with strong hypnotic action. Some practitioners question, however, whether the anxiolytic actions of this medication are as profound as those of the benzodiazepines. In comparison with triazolam, zolpidem is less amnesic, provides less muscle relaxation, yet produces the same somnolence.

One of the greatest advantages and indications for zolpidem is in a busy dental practice, when a patient suddenly decides they would benefit from some anxiolysis. The rapid onset of sedative effects makes this an ideal consideration for an oral "rescue" medication in appropriate situations. Therefore, zolpidem is recommended for situations in which a rapid onset is advantageous and when amnesia is not necessary. Zolpidem is supplied as 5- and 10-mg capsules. Zolpidem is typically administered in a 10-mg dose at bedtime the night before the procedure to insure a good night's sleep, or the same dose 20 minutes before the procedure. It carries a Pregnancy Risk Category B.

Antihistamines

As commonly recognized, a side effect of antihistamines is sedation. Many dentists have come to rely on antihistamine-induced sedation, especially for treating pediatric patients. Although diphenhydramine (Benadryl®) is a good oral sedative for infants and toddlers, dentists more typically

administer either promethazine (Phenergan®) or hydroxyzine (Vistaril®, Atarax®) for children and preteens. Orally administered antihistamines have limited efficacy for producing sedation. One method for improving the efficacy of orally administered antihistamines is to coadminister them with other sedatives. One popular antihistamine-containing "recipe" consists of meperidine, hydroxyzine, and scopolamine (also known as "DVS," an abbreviation for "Demerol®, "Vistaril®," and scopolamine). As discussed earlier, however, sedative combinations such as this one are classified as multi-agent sedation techniques and require more advanced training in conscious sedation and a special permit in most states and regions.

Promethazine is supplied as an elixir (5 mg/mL) or as suppositories (25 and 50 mg). The typical dose is 25–50 mg 1 hour before the procedure, resulting in a duration of sedative action approximately 4–5 hours in length. Hydroxyzine comes as a 2-mg/mL elixir and is typically administered at 2–4 mg/kg, (maximum dose of 75 mg). Hydroxyzine often works best in divided doses: 50 mg at bedtime the night before a procedure, 50 mg the morning of the appointment, and 50 mg 1 hour before the appointment. The duration of action for hydroxyzine is approximately 6 hours. Diphenhydramine is formulated as 25- and 50-mg tablets. Administering 25–50 mg 1 hour before the procedure results in adequate sedation.

As single oral agents, the antihistamines work well to produce a light and mild sedation with mostly somnolence. Although they are typically used to produce sedation with pediatric patients, their sedative effects are similar when used for adults. The most predictable and clinically useful sedative effects occur when antihistamines are combined with other sedative agents, requiring additional training and a special permit in most states and regions.

Barbiturates

The use of barbiturates (eg, pentobarbital, secobarbital) for their sedative properties has largely fallen out of favor in dentistry, and for good reason. Although the general mechanism by which barbiturates produce sedation at $GABA_A$ receptors is similar to that of the benzodiazepines, there are some important differences. Rather than binding directly to the $GABA_A$ receptor, barbiturates bind to another site on the $GABA_A$ receptor complex (not the omega receptor binding site used by benzodiazepines). Although barbiturate binding at this site also increases the binding affinity of GABA for its binding site on the $GABA_A$ receptor complex, the end result at the chloride channel is slightly different [19,25,26]. Rather than increasing the frequency at which the chloride channel opens like the benzodiazepines, barbiturates increase the duration of the channel opening, resulting in neuronal hyperpolarization. Unfortunately, barbiturates also have a direct effect on the chloride channel of the $GABA_A$ receptor complex. At higher doses, barbiturates can open the chloride channel directly, not requiring GABA. This direct

mechanism makes it more likely that profound depression of the patient's CNS can occur, and if not recognized early and managed properly, severe disability, even death, can occur. Thus this class of sedatives is inherently more dangerous and does not offer any significant advantages. Accordingly, we do not recommend the use of enteral barbiturates in the dental setting unless there is physiologic monitoring of the patient's respiratory and cardiovascular systems and the dentist has sufficient advanced training in managing deeper levels of sedation and the complications that might be expected with profound CNS depression.

Administration technique and recovery

The induction of anesthesia with orally administered sedatives is not technically difficult because it only involves the swallowing of a pill or elixir by the patient. The timing of sedative administration in relation to when the dental treatment is to begin can be the greatest challenge. Ultimately, one would like the plasma concentrations of the sedative to be within the therapeutic range during the dental treatment. One would especially like the plasma concentrations of the sedative to be at their greatest during those parts of the treatment in which sedation helps the patient cope and the dentist perform the treatment. Decisions about when the sedative is to be taken by the patient should be based on the time required to reach peak plasma concentrations and when during the treatment this would be most beneficial. As was probably clear in the earlier sections on the individual oral sedative, the latency to reach peak plasma concentrations can be highly variable. Oral sedatives with latencies between 30–60 minutes have the greatest practicality for dentistry.

The latency for reaching plasma concentrations in the therapeutic range requires the dentist to make one important decision, specifically, should the sedative be taken at the office or at home (or en route to the office). Although there is great convenience in having the patient medicate on their own outside of the office, it is our recommendation that the patient take the sedative in the controlled environment of the dental office for reasons that involve risk management, for example, assessing the patient's baseline status and the effects (desired and undesired) of the sedative. Measuring and recording baseline vital signs is highly recommended immediately before administering any pharmacologic agent, especially sedatives. After verifying that the baseline vital signs are within normal limits and that all of the details surrounding the sedation have been taken care of (signing of consent documents, knowing that an adult escort will be present when the patient is to be dismissed), it is time to administer the sedative. By having the patient take the sedative in the office, one is also more sure about their level of compliance and understanding of the dosing instructions, such as when to take the medication and how much to take. The name of the sedative, the dose administered, and the time of administration need to be documented in the

patient's chart. The patient should not be left unattended after taking the sedative. A family member, escort, or member of the office staff should be with the patient at all times.

Dental treatment delivery should begin once the patient reaches a comfortable level of sedation. The signs of sedation vary depending on the personality of the chosen sedative. Sometimes it takes a little longer than expected for the patient to reach this comfortable level of sedation, so patience may be warranted. If indicated, the efficacy of the oral sedative can be enhanced by the careful addition of nitrous oxide and oxygen in the manner described earlier. By varying the titration of N_2O/O_2, the depth of the sedation can be changed quickly on an as-needed basis. A tempting alternative method for increasing the efficacy of an oral sedative is to administer another dose of the same sedative. Considering the latency to reach therapeutic plasma concentrations, oral re-dosing is not practical. Additionally, there are likely to be situations in which this practice induces a greater level of CNS depression than is indicated or safe, which can be especially problematic if this occurs after the procedure's completion. Remember, the patient is to remain conscious, respond appropriately to verbal commands and stimuli, and maintain their protective reflexes. Failure to maintain any or all of these characteristics would suggest that an excessive amount of CNS depression is present and the patient's safety is in jeopardy unless the dentist has sufficient advanced training in managing deeper levels of sedation. Accordingly, we do not endorse the practice of re-dosing with any oral sedative as a method for increasing the efficacy or depth of the sedation.

Methods for monitoring physiologic status of the patient sedated with PO agents need to be in place during the procedure. The most important physiologic parameters that need monitoring include the level of CNS depression and the adequacy of respiratory function and ventilation of the lungs. Monitoring the status of the cardiovascular system is also important (blood pressure and heart rate), with the realization that it is not one of the organ systems that shows immediate changes as complications develop. Fortunately, the level of monitoring required for the patient who is receiving oral sedatives is not sophisticated, technically difficult to perform or interpret, or invasive for the patient.

Evaluating the patient's level of consciousness is generally sufficient for determining the amount of sedation-induced CNS depression present. As long as the patient retains the ability to respond appropriately to physical stimulation or verbal command, one is working within the range of conscious sedation. It is acceptable during conscious sedation for the latency of the patient's responses to be slower than normal, and their speech to be slurred in some situations.

The next most important physiologic parameter to monitor during sedation is the adequacy of respiratory function and ventilation of the lungs. The most serious of sedation-related complications is usually a consequence of the patient losing the ability to maintain their own airway without assistance.

As long as the patient maintains consciousness, the likelihood of this occurrence is small. If the patient lapses into a state of unconsciousness, however, the tongue and other soft tissues in the oropharynx loose their muscular tone and are able to partially or completely block the patency of the airway. If not corrected by positioning the head in a manner to relieve the blockage, a state of hypoxia develops quickly. There also is a concomitant build-up of carbon dioxide from cellular metabolism when the patency of the airway is blocked, resulting in an acidotic condition. With a prolonged combination of these two insults to homeostasis, the functioning of other systems becomes compromised. Most notably, neither neurons of the CNS nor cells of the myocardium tolerate these physiologic conditions well. Severe brain damage and death are likely consequences if the airway problems are not corrected.

Assessment of lung ventilation during oral sedation is simple and requires no special instrumentation. In the simplest of situations, talking with the patient, watching their chest rise and fall with each breath, feeling the warmth of expired air against your hand when it is passively in front of their mouth or nose, or watching the reflective surface of the dental mouth mirror alternate between foggy and clear when placed under the patients nose are all methods to evaluate ventilation of the lungs. The use of a pretracheal stethoscope connected to the operator's ear is another method for determining the patency of the airway and the rate and depth of the patient's breathing.

Although these methods are useful for determining whether the airway is open and capable of ventilating the lungs, they tell nothing about how well the tissue is being oxygenated. Pulse oximetry measures the percentage of oxygenated hemoglobin by evaluating the ratio of absorbed versus reflected light wavelengths at a peripheral site (fingertip, toe, bridge of the nose, or earlobe). Hemoglobin saturation of normal adults breathing room air is typically 97–100%. Although the hemoglobin saturation is likely to drop slightly in the sedated patient, it should NEVER decrease to less than 90%, because this equates to arterial oxygen tensions that would be approximately 60 mm Hg. Although the pulse oximeter is a valuable instrument for assessing oxygenation, direct techniques like assessing the movement of the chest and listening to the movement of air with a pretracheal stethoscope should be considered the "gold standard."

Dismissing the patient at the end of the procedure should only occur when the patient has recovered sufficiently from the effects of the sedative. Although a return to baseline levels of alertness are not likely because of the pharmacokinetics of oral sedation (eg, redistribution, hepatic metabolism), a certain level of recovery is necessary before dismissing the patient. This should minimally include the ability to hold a coherent conversation demonstrating that the patient is oriented to their surroundings, the ability to ambulate with minimal assistance, and vital signs that are close to those obtained at baseline. Once these criteria have been met, it is acceptable to

dismiss the patient to a responsible adult escort. Documentation that supports your assessment of the patient's return to baseline and the adequate resolution of sedative effects should be recorded, together with any interventions that needed to be performed during the procedure or the recovery. Documentation in the patient's chart also needs to include the name of the adult escorting the patient from the office and the time they are dismissed.

Summary

There are clearly many safe and effective sedatives available to the dental practitioner for reducing patient fear and improving their level of comfort. Careful consideration needs to be given to the objectives of the sedation when deciding which pharmacologic agents to use because they all possess slightly different clinical characteristics and various degrees of risk. Patient selection also is critical when making decisions about sedation because the patient's expectations and general health status factor into keeping the procedure safe.

N_2O/O_2 sedation is an excellent choice for managing the mildly fearful dental patient or when minimal sedation is desirable. Among the sedatives administered enterally, the benzodiazepines are the most commonly used, and for good reason. These drugs are safe, effective, and offer a host of different personalities from which the dentist can choose. If used wisely and thoughtfully, the dentist can tailor the effects and duration of onset and recovery to the needs of the patient and the expected parameters of the appointment. When N_2O/O_2 sedation is combined with a single enteral sedative, a more profound level of CNS depression is achieved that can be modestly altered by changing the concentration of inhaled nitrous oxide.

With these many pharmacologic alternatives, many different dental patient populations can be sedated in a safe, effective manner, thus allowing the delivery of most dental treatments in a setting of reduced psychologic and physiologic stress. These pharmacologic sedatives have truly opened up a wonderful world of possibilities for the comfortable delivery of dental care, and should be integrated into every office's repertoire for delivery of care.

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