Balancing efficacy and safety in the use of oral sedation in dental outpatients

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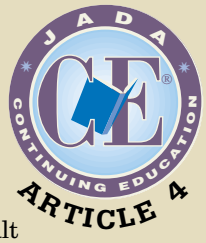
Continuing concerns over the safety of oral sedation in children and new controversies regarding the use of the benzodiazepine (BZ) triazolam for the sedation of dental outpatients prompted a 2003 meeting called "Workshop on Enteral Sedation in Dentistry" and cosponsored by the United States Pharmacopeial Convention, the Anesthesia Research Foundation of the American Dental Society of Anesthesiology and the Dental Anesthesia Research Group of the International Association for Dental Research. In pediatric dental patients, oral sedatives often are administered to control behavior, as well as to alleviate fear and apprehension. This use necessitates patients' receiving relatively large doses of sedative agents that have an increased likelihood of evoking deep sedation and respiratory complications. In addition, some of the drugs commonly used also have extended durations of action, which

ABSTRACT



Background. Concerns about the safety of pediatric oral sedation and the incremental use of triazolam in adults prompted a workshop cosponsored by several professional organizations.

Overview. There is a strong need and demand for adult and pediatric sedation services. Using oral medication to achieve anxiolysis in adults appears to have a wide margin of safety. Mortality and serious morbidity, however, have been reported with oral conscious sedation, especially in young children. Most serious adverse events are related to potentially avoidable respiratory complications.

Conclusions. Clinical trials are needed to evaluate oral sedative drugs and combinations, as well as to develop discharge criteria with objective quantifiable measures of home readiness. Courses devoted to airway management should be developed for dentists who provide conscious sedation services. State regulation of enteral administration of sedatives to achieve conscious sedation is needed to ensure safety.

Practice Implications. Safety in outpatient sedation is of paramount concern, with enteral administration of benzodiazepines appearing safe but poorly documented in the office setting. Conscious sedation by the enteral route, including incremental triazolam, necessitates careful patient evaluation, monitoring, documentation, facilities, equipment and personnel as described in American Dental Association and American Academy of Pediatric Dentistry guidelines.

Key Words. Triazolam; conscious sedation; anxiety; dental pain control.

JADA 2006;137:502-13.

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may place younger children in danger of resedation after they have been discharged.

Triazolam is approved by the U.S. Food and Drug Administration (FDA) for the short-term treatment of insomnia in a dose range of 0.125 to 0.5 milligrams. It is not approved for enteral sedation but is recognized widely by the dental profession as having useful sedative/anxiolytic properties. Use of an approved drug in another dosage form, for another indication, at higher doses, in a different patient population or for a use not mentioned in the original labeling is considered to be an off-label use of the drug. The FDA, however, recognizes that the off-label use of drugs by practitioners often is appropriate and may represent the standard of practice. Examples of off-label uses of approved drugs include many pediatric uses, many drugs used for oncology and therapeutic uses that are recommended by specialty societies. It generally is recognized that BZs have multiple effects, but pharmaceutical sponsors do not always seek regulatory approval for all potential indications.

The primary concern of oral sedation in adults is the emerging use of multidose triazolam.

The primary concern of oral sedation in adults is the emerging use of multidose triazolam. Although a single dose of triazolam administered orally or sublingually (the tablet is placed under the tongue to dissolve) in an amount approved by the FDA for the treatment of insomnia provides effective and safe sedation for moderately anxious patients,[1-5] the administration of incremental doses of the drug, sometimes in combination with other sedative agents, is becoming increasingly popular. Proponents of this approach suggest that it provides a therapeutic alternative for unmet need and demand for sedation services that can be administered safely by dentists who do not have advanced training or hold a permit for parenteral sedation. Opponents have expressed concerns about the possibility of unpredictable central nervous system (CNS) depression in the offices of dentists who are unprepared to manage deep sedation.

The workshop brought together experts in anesthesiology, pharmacology and sedation; representatives from national dental organizations; and people representing a broad spectrum of the dental and medical communities to review the scientific basis and status of oral sedation in dentistry and to recommend research initiatives and regulatory changes that may improve patient care. In this article, we summarize the data presented and opinions expressed by the workshop's speakers and participants.

NEED AND DEMAND FOR ANESTHESIA AND SEDATION SERVICES

Anesthesia and sedation services for dental outpatients commonly are indicated for the management of fear, anxiety and phobia. Need and demand are necessary precedents for delivering these services. "Need" may be defined as a condition or situation in which there is a physiological or psychological requirement for the well-being of an organism. "Demand" can be defined as asking for a resolution of that need. "Anxiety," in this context, is a stress response to an ill-defined or anticipated situation, feelings of threat or anticipation of possible danger. "Fear" is a physiological process that occurs when the person is threatened by more immediate danger. "Phobia," conversely, is a persistent or irrational fear that results in a compulsion to avoid a specific object, activity or situation; it can impede daily function.

Additional specific indications for sedation include patients with cognitive impairment who are unable to cooperate, young or emotionally challenged children who cannot cooperate, patients with motor dysfunction (for example, uncontrollable gagging), and extensive surgical procedures or other situations in which local anesthesia may provide insufficient pain control.

The prevalence of fear and anxiety toward dentistry has been documented internationally in numerous surveys (Table).[6-27] The collective data provide evidence that fear and anxiety toward dentistry are common in all of the cultures assessed and that they usually originate in childhood, persist throughout life, lead to avoidance of dental therapy and contribute to diminished dental health. A recent review of 19 studies concluded that anxiety toward dentistry has remained stable over the past 50 years, despite obvious improvements in pain control, dental materials and less invasive procedures.[28]

Several studies also have assessed the demand for anesthesia and sedation services among dental outpatients. Lindsay and colleagues[20] reported that 31 percent of patients surveyed in the United Kingdom prefer sedation or general

TABLE

Surveys documenting the prevalence of fear and anxiety toward dentistry.

COUNTRY (AUTHORS, YEARS)	NO. OF SUBJECTS	OUTCOMES REPORTED
Australia		
Thomson and colleagues, 1996[6]	1,010	14 percent had a high level of dental anxiety
Canada		
Locker and colleagues, 1991[7]	2,007	4 to 16 percent had a high level of fear/anxiety
Locker and colleagues, 1996[8]	2,729	
Liddell and Locker, 1997[9]	2,609	
Locker and colleagues, 1999[10]	1,420	
Denmark		
Moore and colleagues, 1993[11]	565	4 percent had extreme dental anxiety
Iceland		
Ragnarsson, 1998[12]	1,548	5 percent had a high level of anxiety
Japan		
Weinstein and colleagues, 1993[13]	3,041	21 percent were very afraid or terrified
Jordan		
Taani, 2001[14]	287	6 percent had a high level of dental phobia
Netherlands		
Stouthard and Hoogstraten, 1990[15]	648	11 percent were extremely anxious or phobic
New Zealand		
Thomson and colleagues, 2000[16]	790	13 to 21 percent had a high level of dental anxiety
Singapore		
Teo and colleagues, 1990[17]	288	8 to 21 percent had a high level of dental fear
Sweden		
Hakeberg and colleagues, 1992[18]	620	4 to 7 percent had a high level of fear
Hagglin and colleagues, 1996[19]	1,016	
United Kingdom		
Lindsay and colleagues, 1987[20]	419	15 percent were very or extremely anxious
United States		
Gatchel and colleagues, 1983[21]	105	12 percent had a high level of dental fear
Milgrom, 1986[22]	1,010	20 percent had a high level of dental fear
Gatchel, 1989[23]	1,882	11 to 12 percent had a high level of dental fear
Domoto and colleagues, 1991[24]	419	13 percent were very afraid or terrified
Kaakko and colleagues, 1998[25]	232	19 percent had a high level of dental fear
Doerr and colleagues, 1998[26]	455	10 percent had a high level of dental anxiety
Dionne and colleagues, 1998[27]	400	15 percent were very nervous or terrified

anesthesia, but far fewer patients who prefer these modalities actually receive them. A survey conducted in the United States found that 18 percent of adults would visit the dentist more frequently if they were given a drug to make them less nervous.[27] This survey also found a threefold discrepancy between the number of patients who would prefer to receive anesthesia or sedation and the availability of these services. Surveys in Jordan[14] and Canada[29] also identified unmet demand for anesthesia and sedation services in a portion of the population (12-14 percent), with a nearly threefold greater interest in receiving services among those who reported themselves as being highly fearful. The anticipated invasiveness/stressfulness of the procedure dramatically increases demand for anesthesia/sedation services, with preference rising from 2 percent for a routine dental cleaning to 47 percent for a tooth extraction to 55 percent for an endodontic procedure to 68 percent for periodontal surgery.[29] The available evidence indicates that there are both need and demand for anesthesia and sedation services that are not well-met.

CLINICAL CONSIDERATIONS IN THE MANAGEMENT OF THE CARE OF PEDIATRIC DENTAL PATIENTS

Traditional management-of-care techniques for children still are prevalent, but they are limited

largely to behavioral management techniques, enteral sedation and general anesthesia. A 2001 survey of pediatric dentists indicated that children are less cooperative than in past years, and it attributes this finding to changes in parenting styles, primarily a failure of parents to set limits on children's behavior.[30] Issues that also contribute to management problems include the large number of carious lesions in children of lower socioeconomic status and the perception that children cry and struggle more readily in the dental office. The wait for general anesthesia or sedation services that children with management problems have had has increased in some areas of the country to approximately one to two months.[31]

Management of the care of pediatric dental patients is evolving into three categories: behavioral management with "tell, show, do"; sedation with nitrous oxide and oxygen inhalation or oral midazolam; and general anesthesia. Recommendations to improve clinical practice include modification of training programs to address patient safety; broadening research activities to include comprehensive clinical trials; better exchange of experiences among medical and dental practitioners; and development of specific sedation regimens for autistic, hyperactive and obese children and for young patients with asthma or seizure disorders.

Evaluation of the safety of enteral sedation for children in the dental office is limited by deficiencies in quantitative morbidity and mortality data.

SAFETY OF ENTERAL SEDATION FOR CHILDREN

Evaluation of the safety of enteral sedation for children in the dental office is limited by deficiencies in quantitative morbidity and mortality data. These deficiencies include underreporting of adverse events, overreporting of adverse events with new drugs, incomplete documentation, lack of overall usage rates and changing clinical practices over time. The use of enteral sedation has been influenced over the past two decades by changes in state regulations, adoption of national usage guidelines, and improvements in training programs and sedation protocols. For example, in a 1980 survey,[32] opioids were identified as the drug class most commonly used for dental sedation usually in combination with hydroxyzine or promethazine. This type of sedation had a four to six times greater incidence of adverse events than did sedation without use of an opioid. Consistent with the pharmacology of opioids, a dose-dependent increase in untoward outcomes, including hypoxemia (hemoglobin oxygen saturations below 90 percent), was documented for meperidine.[33] Sedation using oral transmucosal fentanyl has been shown to provide similar results regarding adverse events.[34] The supra-additive interaction between opioids administered for sedation and local anesthetics given for pain relief can magnify respiratory depression and the likelihood for serious morbidity or mortality.[35,36] Studies also have demonstrated the potential for adverse drug interactions resulting in respiratory depression when an opioid is used in combination with other sedative drugs.[37]

Chloral hydrate still is used for pediatric sedation by dentists despite its high incidence of adverse reactions, concerns related to its tendency to cause mucosal irritation and its dysrhythmic and possibly carcinogenic potential.[38-40] Although a retrospective chart review of 195 administrations of chloral hydrate (50 mg/kilogram) in combination with meperidine and hydroxyzine judged the sedation as satisfactory in 72 percent of cases and with adverse events occurring at a low frequency,[41] a survey of 616 pediatric dentists reported two episodes of significant respiratory depression associated with chloral hydrate.[42] While higher doses of chloral hydrate combined with nitrous oxide appear to provide improved sedation, the increasing CNS depression can produce deep sedation or general anesthesia easily and lead to airway obstruction and respiratory depression.[43,44] Of course, even BZs such as midazolam can produce similar results when given in excessive doses.

These data support several generalizations. Deeper levels of enteral sedation induced by excessive single or repeated doses should be avoided. Multiple-drug regimens should be used with caution. The risks inherent in the pharmacological properties of each drug used should be recognized, and the additive systemic effects of the local anesthetic dose should be considered, especially when combined with large doses of sedative agents.

Morbidity and mortality. A retrospective study of morbidity and mortality associated with pediatric sedation used four outcome measures:

death, neurological injury, prolonged hospitalization or no harm to the patient.[45] Of the 95 cases included for full review, 60 resulted in death or neurological injury, and 35 resulted in prolonged hospitalization or no harm to the patient. The most common causes associated with the episodes were related to drug interactions or overdoses, with drugs from six different classes administered alone or in various combinations. All routes of administration were associated with deaths: intravenous (n = 60), oral (n = 37), rectal (n = 9), nasal (n = 4), intramuscular (n = 31) and inhalation (n = 13). Multiple routes of administration were used in many patients, making the total number of routes of administration greater than the number of deaths. The most common event was respiratory depression, which often progressed to cardiac arrest. Dentistry was associated with 29 deaths, followed by radiology with 11 deaths and cardiology with three deaths. The use of pulse oximetry resulted in significantly fewer deaths or injuries in the hospital setting but not in the office setting. Researchers concluded that the drugs used, route of drug administration and patient population were less important to the morbidity and mortality evaluated than were the monitoring and resuscitative skills of the provider. Used appropriately, pulse oximetry is essential, as well as more likely than the anesthesiologist or capnograph to detect respiratory insufficiency first.[46] For early detection to enhance patient safety, however, the clinical team must be prepared to manage the care of patients who are not breathing or whose airways are obstructed.

Comparative outcomes analysis of procedures performed in physician offices and ambulatory surgery centers in Florida attributed a 10-fold greater mortality to office-based procedures.[47] A closed-claims analysis also reported significantly higher incidence of deaths for procedures performed in offices than in ambulatory surgery centers.[48] Based on these data, one of the workshop speakers (C.J.C.) recommended that systematic clinical trials be used to evaluate oral sedative drugs and combinations and that training centers for enteral sedation be established across the country for dentists and physicians.

Delayed recovery and discharge criteria. Aside from the many advantages of enteral sedation, erratic and unpredictable absorption can lead to delayed onset and prolonged recovery. This, combined with difficulty in attempting to titrate to an endpoint when giving a drug orally, can lead to a patient's progressing inadvertently down the continuum of CNS depression from minimal-moderate sedation to deep sedation and general anesthesia. Deeper levels of sedation can be managed if they are recognized by an appropriately trained health professional, but not after the patient is discharged, especially if the patient is released prematurely. Discharge criteria may contribute to avoidable morbidity by permitting the release of sedated patients before they can maintain their airway safely without professional supervision.

Delayed recovery after pediatric oral sedation has not been well-studied. In 1993, a large case series (n = 549) reported that 8 to 19 percent of orally sedated patients either slept more than eight hours after a magnetic resonance imaging (MRI) procedure or were drowsy or unsteady for more than eight hours once they were awake,[49] which was suggestive of prolonged sedation after a single dose of oral sedative. Another case series of 119 children who underwent computed tomography (CT) or MRI while receiving chloral hydrate in a dose range of 47 to 100 mg/kg reported that 30 percent of the subjects did not resume normal activities for more than eight hours, 68 percent of the subjects were unsteady after discharge, and 15 percent vomited.[50] A case series of 376 children who were sedated with either midazolam or chloral hydrate before undergoing MRI or CT showed a significant incidence of gastrointestinal (GI) effects (23 percent), motor imbalance (31 percent) and the need to escalate care (4 percent) after hospital discharge.[51] Chloral hydrate was more commonly associated with GI effects, motor imbalance and agitation than was midazolam. Overall, 5 percent of children who received chloral hydrate did not return to normal functioning until two days later.

The available data suggest the need for stringent discharge criteria with objective measures for assessing discharge readiness. Published criteria for discharge readiness in national guidelines[52-54] often are nebulous and leave room for observer interpretation and bias. Many observational tools have been proposed, and objective measures are being validated. The bispectral index (BIS) monitor continuously evaluates the electroencephalogram (EEG) and computes a single number on a scale of 0 (coma) to 100 (awake) that correlates well with depth of sedation and anesthesia in adults and children.[55] Com-

parison of the BIS to observer rating scales of sedation revealed that 29 percent of children had BIS values approaching deep sedation when they were discharged using observer ratings. Revising the criteria for observer ratings raised BIS scores to the equivalent of minimal or moderate sedation at discharge. In the absence of a gold standard to assess discharge readiness, premature release to an unmonitored setting remains the weakest link in the care of sedated children. Current subjective discharge criteria need to be replaced with objective and quantitative methods that provide a consistent measure of when the child is ready to go home.

CLINICAL CONSIDERATIONS IN THE USE OF ENTERAL SEDATION IN ADULT DENTAL PATIENTS

The need to treat fearful adults has made the effective control of anxiety and pain an integral part of dental practice, enabling dentists to provide health care to millions of people who otherwise would remain untreated. Prudent risk management indicates that dentists should limit the use of sedation to those patients who require the modality after careful screening and that only practitioners with adequate training, monitoring equipment and emergency preparedness should administer sedation. Safety in the ambulatory environment often is based on the perception that only reasonably healthy patients are being treated. Advances in medical care, however, have resulted in dental outpatients who are both medically and pharmacologically complex; the stress and anxiety of a dental procedure may precipitate a medical emergency or urgency outside the scope of a dentist's management expertise. Sedation can be considered as an adjunct in the treatment of such patients to minimize stress and the resultant autonomic response.

The need to treat fearful adults has made the effective control of anxiety and pain an integral part of dental practice.

The anxiolytic efficacy of orally administered triazolam in doses of 0.25 to 0.5 mg is approximately equivalent to that of parenterally administered diazepam in a dosage of 10 to 20 mg.[1,56] Triazolam's relatively fast onset, short elimination half-life, and minimal respiratory and cardiovascular effects make it desirable for outpatient use compared with other sedatives that have less favorable pharmacodynamic and pharmacokinetic properties. The use of an orally administered drug avoids exacerbating anxiety in patients who are fearful of venipuncture. The cost of care also is substantially less for an orally administered agent compared with that involving a parenterally administered sedative. When enteral sedation with a BZ such as triazolam is used in the context of appropriate standards of care, the interests of the public and the profession are served by providing a cost-effective service that can be widely available.

Pharmacokinetics of enteral sedation. An orally administered drug is exposed to metabolic clearance mechanisms in the intestine and liver before it gets into the circulatory system and eventually to receptors to produce its pharmacological effects. By comparison, an intravenously administered drug is deposited directly into the circulatory system. Orally administered BZs have been used since the introduction of chlordiazepoxide (Librium, INC Pharmaceuticals, Costa Mesa, Calif.) in the 1960s; zolpidem tartrate (Ambien, Sanofi-aventis, Bridgewater, N.J.), which is a BZ-like drug, is the most widely used hypnotic in the world. All BZ agonists act through the γ-aminobutyric acid receptor complex to produce their effects.[57] Primary therapeutic effects include anxiolytic/antipanic activity, anticonvulsant effects, induction of sleep and muscle relaxant properties (at oral therapeutic doses). Secondary adverse effects include memory impairment, which may be considered therapeutic in the dental setting; somnolence; and psychomotor impairment. Tertiary effects include changes in EEG beta wave activity and effects on cortisol and growth hormone.

BZ agonists have different receptor affinities; they are reflected inversely by the drugs' different clinical dosages (that is, triazolam has high affinity, and low doses are used clinically). Differing potencies are only quantitative in nature; they do not reflect any qualitative difference in neuroreceptor or neurochemical properties. Realistic hazards of taking BZs fall into three categories: negative pharmacological actions, the potential for drug dependence, and abuse or misuse of the drugs. BZs' ability to produce drug dependence and lead to drug abuse has been exaggerated; abuse is more related to the characteristics of the abuser than the to drug class.[58] The trend in the development and use of BZs is

toward drugs with short half-lives and inactive metabolites and away from drugs with long half-lives and active metabolites. Short half-life drugs have, in general, a more favorable benefit-to-risk ratio.

A pharmacokinetic principle of drug action is that the blood concentration is proportional to the receptor site concentration, which, in turn, governs receptor occupancy and the resultant clinical effect. If the drug concentration is too low, there is a lack of efficacy; if it is too high, toxicity is likely. The desired therapeutic effect is contingent on achieving the correct concentration in the blood and at the receptors.

Triazolam was introduced in the early 1980s. It is not qualitatively different from other BZ agonists, and reports of unusual adverse reactions have not been supported by scientific evidence. CYP3A enzymes in the intestines and the liver metabolize triazolam. Triazolam has about 45 percent oral bioavailability, and its high clearance rate contributes to its short half-life. There is individual variability in metabolism, resulting in about 50 percent variability in clearance of the drug after a fixed dose. Certain drugs can influence triazolam metabolism. Antiretroviral agents, for example, inhibit CYP3A, resulting in a twofold increase in plasma concentrations and a 20-fold greater area under the curve over time.[59]

There is a finite delay in drug equilibration between plasma and brain concentrations of 10 to 15 minutes after administration of 0.25 mg triazolam. There also can be a two- to threefold range in plasma concentrations after administration of oral triazolam,[60] resulting in varying peak plasma concentrations and concentrations over time between people given the same dose. The peak plasma concentrations occur about 15 to 30 minutes sooner than the central effects of the drug, as measured by the EEG. These attributes of triazolam suggest that administering additional amounts of the drug at time points less than one hour on the basis of the patient's sedative response would result in additional dosing while the central effects of the original dose still are increasing. By the time the increased concentration of drug from the second dose is achieved in the plasma and eventually at the active site, oversedation may be produced by the delay in CNS effects.

Applying the properties of orally administered triazolam to make dentistry more acceptable to patients has to take into consideration the drug's absorption half-life (≈ 15 minutes), equilibration half-life (≈ 14 minutes) and elimination half-life (two-three hours). Sublingual administration is based on the observation that it results in a 28 percent greater bioavailability compared with oral administration, in turn resulting in higher plasma concentrations at one to two hours after the drug is administered. Using these data, the administration of incremental doses of triazolam can be modeled. Oral administration of a single 0.25-mg dose results in peak plasma concentrations of approximately 2 nanograms/milliliter at one hour, with a predicted peak at the effect site at one and one-half hours. Sublingual administration of a second 0.25-mg dose at one hour after the first dose results in a doubling of the peak concentrations in the plasma and at the effect site. Administration of a third dose at one and three-quarters hours results in further increases in peak concentrations. The existing data for enteral administration of triazolam combined with modeling based on aggregate data support the concept of achieving greater drug levels at the effect site with subsequently greater pharmacological effects. These data are based on aggregate data, not individual responses, and they do not incorporate the effects of tolerance. The delay in drug equilibration between the plasma and the effect site predicts possible overdose if additional doses are administered on the basis of assessments of the patient's anxiety level, while the plasma concentration still is rising after a prior dose.

Multidose enteral sedation: methods, efficacy and safety. The Dental Organization for Conscious Sedation (DOCS) has developed and taught the use of multidose enteral sedation with triazolam to more than 3,000 dentists over the past several years. The safety considerations for use of the organization's clinical protocol are summarized in Box 1. The recommended treatment protocol is initiated with an orally administered dose of 0.25 mg of triazolam one hour before the appointment; this dose is reduced to 0.125 mg for elderly patients and patients who are considered to be overly sensitive to sedative drugs.

A responsible adult companion needs to escort the patient to the dental office before treatment begins. The dentist should assess the patient on arrival, and additional triazolam can be administered sublingually if needed. The patient should be seated in the operatory and monitored continuously for heart rate and oxygen saturation and for

blood pressure and level of consciousness at five-minute intervals. After 30 to 45 minutes, the patient's level of sedation should be reassessed, and additional triazolam should be given sublingually if required. The stated goal of incremental administration of triazolam is to achieve the lowest appropriate dose for a comfortable visit. Just before the start of treatment, 20 to 30 percent nitrous oxide should be introduced and the local anesthetic administered. Then the nitrous oxide should be discontinued and the dental procedure begun. The patient should be monitored every five minutes, including for verbal responsiveness, while the treatment continues for one to two hours. For appointments longer than two hours, the patient should be reassessed and additional triazolam administered if the patient and dentist agree that the level of sedation no longer is adequate. When the dental procedure is complete, the patient should be dismissed only when the dentist has judged that he or she has recovered sufficiently (for example, is ambulatory and able to converse normally). The patient must be escorted and driven home by the responsible companion, who is properly informed of the postoperative care.

BOX 1

Safety considerations for use of Dental Organization for Conscious Sedation's protocol.

PATIENT SELECTION CRITERIA
- Complete medical history and drug history
- Age (adults only)
- American Society of Anesthesiologists (ASA) classification (ASA I and II)

TRAINING
- 18 hours and 20 clinically oriented experiences with patients
- Airway management
- Basic life support training for all clinical team members
- Continuing education requirements to maintain competency

EQUIPMENT
- Pulse oximeter
- Automatic blood pressure monitor (five-minute intervals)
- Portable positive pressure oxygen delivery system
- Masks appropriate for patient population

EMERGENCY PREPAREDNESS
- Emergency protocols
- Emergency kit
- Flumazenil
- Naloxone

To assess sedation level for determining the need for additional medication, the dentist should sit at eye level with the patient and ask the patient to rate the level of sedation using a 10-point scale (1 = relaxed, 10 = excited). The patient's ability to make eye contact and his or her speed in answering and quality of speech should be evaluated to determine if additional medication is required. The dentist also should ask the patient if more sedation is desired. If there is no sign of clinical effect, a 0.5-mg dose should be administered; a 0.25-mg dose should be given only when a slight sedative response is observed, and a 0.125-mg dose should be given when mild sedation is observed. No additional medication should be given when acceptable sedation is noted, as judged by the patient or dentist.

No additional medication should be given when acceptable sedation is noted, as judged by the patient or dentist.

Recommended training for use of the DOCS enteral sedation protocol is consistent with relevant American Dental Association (ADA) guidelines: 18 hours of didactic training plus 20 clinically oriented patient experiences. Clinically oriented experience is defined as a direct, indirect (that is, filmed or videotaped) or simulated patient exposure intended to teach the student recognition, management of the care of and treatment of a sedated patient. All team members should be certified in basic life support. The dentist administering the sedative should have evidence of training that satisfies state board certification and continuing education requirements.

As with other forms of sedation used in dentistry, prospectively collected morbidity and mortality data are lacking for enterally administered triazolam. A retrospective survey of DOCS-trained dentists, however, provides an approximation of clinical outcomes over a 12-month period. A total of 613 dentists administering incremental triazolam reported 85 adverse reactions in 28,881 cases (0.3 percent incidence). None of the instances resulted in the need for hospitalization, and the administering dentists managed all of the instances in the dental office. Fifteen episodes involved blood oxygen saturation less than 90 percent for at least two minutes continuously or repeatedly dropping below 90 percent for shorter periods, 18 episodes involved elevated systolic blood pressure (> 200 millimeters of

mercury), five involved hypotension (defined as decrease in blood pressure below 75 percent of baseline), and 10 episodes involved tachycardia or bradycardia. An additional 37 cases were considered adverse outcomes owing to the failure to maintain satisfactory levels of conscious sedation. Nineteen cases involved the administration of flumazenil. There were no reports of mortality. Although these data are retrospective and did not use an accepted sampling method to rule out data selection, they form the basis for more formal morbidity and mortality monitoring to assess the safety of incremental enteral sedation with triazolam.

BZs are regarded as being extremely safe in clinical use, and there is a wide margin between therapeutic doses and toxic doses. The median lethal dose for oral triazolam in some animal models exceeds 1,000 mg/kg. The relatively few case reports of mortality that are associated with triazolam usually refer to suicide attempts in which the maximum recommended dose was exceeded at least 10-fold and commonly involved the ingestion of alcohol or other CNS depressant drugs.

Does the enteral route of administration confer greater safety? The oral route is inherently the safest route for drug administration. Protection is provided against foreign substances by the vomiting mechanism, first-pass elimination and a muted anaphylactic response. The relatively slow absorption reduces distributional influences and allows for recognition of deleterious trends and the possibility to prevent further absorption. The oral route also avoids local damage associated with needle puncture, ischemia from intra-arterial injection and venous irritation leading to thrombophlebitis. Conversely, variables influencing drug absorption—including gastric emptying, GI absorption, GI inactivation, first-pass hepatic metabolism and variability in patient response associated with using fixed doses—often raise safety concerns that limit dosing and drug efficacy.

Based on these considerations, the administration of two 0.25-mg doses of oral or sublingual triazolam separated by time should be safer than the administration of a single 0.5-mg dose. Multiple dosing can prolong the duration of effect and provide limited ability to titrate the dose to achieve the desired effect. Sublingual administration of triazolam should produce a faster onset and enhance titration ability by reducing some of the variables associated with oral administration. The dosing interval for titrating triazolam, however, has not been established, nor have the relationships between the plasma concentration, effect-site concentration and observed sedation. Finally, the balance between acute tolerance to the sedative effects of multiple doses and their combined toxic effects is not clear. Available data suggest that while there is a good relationship between plasma concentration and observer-rated sedation over the first two hours after administration of a 0.25-mg dose, a dissociation occurs as the drug effect falls more rapidly than does the plasma concentration.[61] Acute pharmacodynamic tolerance to triazolam has been demonstrated most clearly by studies in which the psychomotor effects of the drug dissipate over several hours even as the plasma concentration is held constant.[62]

Reversal of BZ sedation by flumazenil. Flumazenil is a high-affinity "neutral ligand" that only acts as an antagonist when it displaces or prevents binding of an agonist ligand. The duration of BZ reversal by intravenous flumazenil is relatively short, and resedation can occur, especially if the BZ is long-acting. The effect of flumazenil administered by other routes, including the sublingual injection route favored by proponents of triazolam titration, is not well-studied.

The intramuscular, subcutaneous and sublingual routes of flumazenil injection have been studied in dogs.[63] Although reversal of midazolam-induced respiratory depression was successful with all injection methods, the mean reversal time was significantly shorter with intravenous administration (120 versus 262 seconds with sublingual administration).

CONCLUSIONS

Data presented by workshop speakers and participants revealed numerous areas of consensus (Box 2). Foremost among these were the general agreement that there is a strong need and demand for enteral sedation services in dentistry that are not always met by available resources; the oral route is convenient, suitable and widely accepted in dentistry; and patient safety, a paramount concern must at least equal that of the most common therapeutic alternatives (general anesthesia in the hospital or surgery center for children and intravenous sedation in the office setting for adults).

Although the enteral route appears to be safe, especially when used for anxiolysis in adults, the ability to draw firm conclusions on this issue was hampered by a relative lack of reliable safety data. Large-scale prospective studies are needed, including comparative outcome studies that examine the influence of sedation provider, treatment location and selection of agents, especially multidose and multidrug regimens.

The workshop participants regarded proper education as a key element in promoting availability and safety of enteral sedation in dentistry. There was general agreement that increased educational opportunities should be available at the predoctoral, postdoctoral and continuing education levels and that this training should at a minimum follow the ADA's Guidelines for Teaching the Comprehensive Control of Anxiety and Pain in Dentistry pertaining to enteral sedation.[64] Courses preparing dentists to provide enteral sedation for children should include relevant instruction in pediatric anatomy, pharmacology, physiology, sedation techniques and emergencies. Courses describing multidose enteral sedation techniques in adults should compare the pharmacokinetics and pharmacodynamics of sedative agents administered in single versus multiple doses. Because respiratory emergencies, which can be avoided and normally are manageable, account for the vast majority of serious adverse responses to enteral sedation, a specific airway management course should be developed for providers to supplant or even replace the traditional advanced cardiac life support course.

With the exception of anxiolytic drugs given orally to adults and teen-agers as a single dose or a series of smaller doses whose total amount does not exceed the maximum recommended dose for prescription use, enteral conscious sedation should be regulated by state dental boards to ensure that providers have the necessary training (as described previously); use appropriate patient evaluation and monitoring methods; provide proper documentation, including written informed consent; and maintain required equipment, supplies and personnel as described in the ADA's Guidelines for the Use of Conscious Sedation, Deep Sedation and General Anesthesia for Dentists.[65] The courses taken to meet the educational standards and the course instructors who teach them should be approved by the dental boards or other appropriate agencies. A regular continuing education requirement also should be mandated.

BOX 2

Workshop on Enteral Sedation in Dentistry findings.

GENERAL CONCLUSIONS

- There is a strong need and demand for adult and pediatric enteral sedation services.
- Patient safety is the paramount consideration.
- Oral medication to achieve anxiolysis in adults appears to have a wide margin of safety.
- Anxiolytic drugs given orally as a single dose or as an aggregate of smaller doses at or below the maximum recommended dose for prescription use should remain unregulated.
- Mortality and serious morbidity have been reported with oral conscious sedation, particularly in young children.
- Most serious adverse events are related to respiratory complications and are potentially avoidable.
- Existing guidelines for pediatric sedation should improve safety, if universally followed.
- Enteral conscious sedation, including incremental triazolam techniques, necessitates evaluating patients, monitoring, documentation, facilities, equipment and personnel requirements as described in American Dental Association (ADA) guidelines.*
- Enteral administration to achieve conscious sedation requires state regulation to ensure safety.

RECOMMENDATIONS FOR TRAINING

- Minimal educational standards for enteral conscious sedation, including pediatric sedation and incremental triazolam techniques, should be mandated as described in ADA guidelines.†
- Courses offered to meet educational standards should be approved for content by an appropriate agency (for example, the state dental board).
- Continuing education courses should be mandated at regular intervals.
- A specific airway management course to supplant or replace advanced cardiac life support should be developed for enteral conscious sedation providers.
- Increased educational opportunities at the predoctoral, postdoctoral and continuing education levels should be provided for enteral conscious sedation.

STRATEGIES TO ENHANCE SAFETY

- Establish a national data clearinghouse to create a comprehensive database of morbidity and mortality related to anesthesia and sedation.
- Enhance transorganizational communication to promote greater safety, improved training and quality assurance/quality control in the use of anesthesia and sedation.
- Develop and adopt specific discharge criteria to avoid mortality/serious morbidity associated with resedation at home.

RESEARCH NEEDS REGARDING ENTERAL SEDATION

- Safety of enteral sedation as determined by large-scale prospective clinical trials.
- Comparative studies of anesthesia and sedation in hospitals, surgery centers and office settings.
- Pharmacokinetic/pharmacodynamic relationships of incremental triazolam dosing.
- Individual responder analysis for titrating triazolam dose for efficacy and safety.
- Safety of multidrug regimens for enteral sedation in children and adults.
- Flumazenil indications, doses and routes of administration for reversing the effects of enteral sedation.

* American Dental Association.[65]
† American Dental Association.[64]

Findings pertaining to the use of enteral sedation in children stem from the reported documentation of mortality and serious morbidity, especially in young children. There was consensus among workshop participants that safety would be improved significantly if existing guidelines for the delivery of pediatric sedation services were followed universally. In addition, objective measures of recovery to home readiness should be sought to prevent resedation in an uncontrolled environment. Until such measures become available, discharge criteria should include requirements that the child continuously maintain a patent airway and remain spontaneously awake without stimulation.

Recommendations pertaining to adult enteral sedation arise from the lack of data about the pharmacokinetic and pharmacodynamic relationships of incremental triazolam dosing. Future studies should include the influence of dosing amounts and intervals on plasma and effector site concentrations. They also should include how these variables influence therapeutic and potentially toxic drug responses, as modified by the possible development of acute tolerance to some but perhaps not all of the effects of triazolam.

Finally, participants expressed differing opinions about the delayed onset of BZ reversal by flumazenil administered nonintravenously. Some workshop participants felt that providers of enteral conscious sedation, including those administering triazolam incrementally, must be trained to administer flumazenil intravenously, whereas others believed that the onset of reversal by the sublingual or intramuscular route is sufficiently fast to manage emergencies if the patient is monitored at regular intervals for responsiveness to verbal command. All of the participants agreed that there is an urgent need to define the pharmacological characteristics of flumazenil administered by nonintravenous routes and to ascertain if the resultant antagonistic action is quick and strong enough to reverse signs and symptoms of triazolam overdose as may occur with incremental triazolam dosing. ■

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