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Common Benzodiazepines

A thorough review of dental anesthetics and their reversals

by Tammy Smit, CRNA

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Course description

Sedation for dental treatments and procedures is on the rise, and is often expected by patients. Practitioners offering sedation often request additional information on commonly used pharmaceutical agents. The benzodiazepine class of medications is the most commonly used type of medication used for either oral or intravenous sedation. This course revisits the pharmacology of these prescribed sedatives, including midazolam, diazepam and triazolam.

Objectives

Upon completion of this course, the participant should be able to achieve the following:

1. Identify the incidence of dental anxiety.
2. Discuss the advantages of benzodiazepines that make them an attractive choice for dental sedation.
3. Give examples on how benzodiazepines exert their effects in the central nervous system.
4. Interpret the American Society of Anesthesiologists Physical Status Classification and its relationship to dental sedation.
5. Recognize levels of anxiety through the indicator of sedation needs tool to identify the appropriate level of sedation.
6. Identify that age, nutritional status, renal or hepatic disease may require a decrease in dosages of prescribed benzodiazepines.
7. Examine best practices for providing anxiolysis.
8. List contraindications and special considerations when administering benzodiazepines.
9. Review the treatment of unintended benzodiazepine overdose.

Introduction

Pain and anxiety have always been associated with dental treatment. It has been increasingly more common for anxious patients to seek out sedation dentistry; in fact, surveys suggest that around 60% of the population suffers from anxiety, fear or phobia toward dental procedures.[1] Moreover, these anxious behaviors lead to avoidance of care, resulting in compromised dental health. Because of their fears, as many as 5–7% of the population never or rarely visits a dentist.[2] This ultimately causes bad oral health and potentially creates advanced disease states, beginning a cycle of anxiety and declining oral health and making it even more challenging when these patients actually seek dental care.

Not only lived as a frustrating experience by the patients, dental phobia and anxiety also affect dental practitioners. Patient anxiety and declined oral state often lead to reduced patient cooperation and enhanced time of procedures. In addition, dental anxiety could lead to misdiagnosis.[3]

To offer appropriate management for those patients, it is crucial to assess their severity of anxiety disorders. Many standardized questionnaires or a dental anxiety scale can be used to determine a patient's level of anxiety. Determining a patient's level of anxiety helps dentists select the most appropriate benzodiazepine based on the patient's medical history, anxiety, and type and length of the proposed dental treatment.[4]

Regardless of anxiety level (low, medium or high), both psychotherapeutics and pharmacological interventions have shown equal efficacy in dealing with fear in the dentist office. Pharmacological management of anxiety includes many types of sedation and involves a wide entity of anesthetics.[5] Benzodiazepines, with their antianxiety, sedative–hypnotic, anticonvulsant and skeletal muscle-relaxant properties, are commonly used as pharmacological therapeutics to relieve anxiety before dental procedures.[6] But either oral or intravenous use of benzodiazepines requires dentists and dental teams to follow proper guidelines and to be adequately trained to cope with side effects and potential complications from these pharmaceutical agents.

Additionally, it is also necessary to appropriately reverse any unintended benzodiazepine overdose with another pharmaceutical agent, flumazenil. Let's start with the review of benzodiazepines.

Pharmacology of benzodiazepines in dentistry

All benzodiazepines possess anxiolytic, amnesic, sedative, muscle-relaxant and anti-convulsant properties. These properties make benzodiazepines an attractive choice for oral and intravenous sedation in dentistry. Triazolam, midazolam, lorazepam and diazepam remain the most commonly used benzodiazepines. Their effects on the central nervous system (CNS) and their pharmacological properties are well suited for their use in dentistry.

They can be used in either oral or intravenous sedation in the dental office. Before investigating the most commonly used benzodiazepines in dentistry, we will explain the general mechanism of action, physicochemical properties and absorption of various administration routes of benzodiazepines.

Mechanism of action

Specific receptors for benzodiazepines have been identified in the CNS. These receptors are an integral part of the gamma amino butyric acid (GABA) receptor complex.[7] The GABA receptor is an inhibitory neurotransmitter. Stimulation of the GABA receptor with medications like benzodiazepines slows impulses and promotes calmness. The slowing of neural impulses also promotes the benefits of seizure prevention. The mild amnestic effects of certain benzodiazepines make them ideal for sedation during stimulating or painful portions of dental procedures.

Physicochemical properties

Benzodiazepines are low-molecular-weight drugs with lipid solubility characteristics. This allows them to rapidly pass through the central nervous system and exert their calming effects. It is important to consider that benzodiazepines are strongly bound to plasma proteins.[8] They also have an unbound portion that is active in the patient's system—the active portion of the medication. The active portions range from 2–10%, which produces the majority of

the medication's actions in the patient's body. Any decrease in systemic proteins results in a greater availability of free drug in the patient's system to exert its actions. Therefore, patient conditions—typically associated with poor nutritional status, advanced age, or hepatic or renal insufficiency—result in an increase in the free and active form of benzodiazepines. The lack of proteins for binding is an indication for dosage reductions in these special populations.[9]

Absorption: Oral, intramuscular and intravenous

After oral administration, benzodiazepines are usually well absorbed by the gastrointestinal tract. Although this is the case, they take longer to exert their intended effects, and their time to onset may be challenging to coordinate with schedules and dental treatments. Intravenous administration allows a quick distribution to the brain and by the way to the central nervous system. Unlike other benzodiazepines, midazolam and lorazepam are rapidly absorbed intramuscularly; therefore, the intramuscular route remains an alternative for premedication in dentistry when the oral administration is impossible.[10] This route also presents issues in timeliness of absorption and the timing of dental treatment.

With the exception of triazolam, most benzodiazepines can be administered intravenously. This may be the most controllable route of administration of all the possible routes of benzodiazepine administration.

Benzodiazepines and patient selection

A discussion of sedation in dentistry warrants a brief conversation about appropriate patient selection. Patient selection is key in the continuum of sedation.

Patient history, assessment and interview are key components in the appropriate selection of a benzodiazepine for dental sedation. Standard patient history forms and patient interview are familiar to practitioners, and permit dentists to assess a patient's American Society of Anesthesiology (ASA) classification (see Table 1). Studies and assessment tools, like the indicator of sedation needs (IOSN), demonstrate that oral and intravenous sedation may be appropriate sedation techniques for patients who fall under the ASA I and II classifications.[11]

The IOSN provides objective scoring to allow for an appropriate sedation technique (See Table 2, p. 80). It uses information about patient anxiety, medical and behavioral status, and treatment complexity. Scores for each of these indicators range from 1–4 and final scores sum to 3–12. A score of 3 or 4 indicates minimal need for sedation; 5 or 6, moderate need; 7–9, high need; and 10–12 suggests very high need or even use of general

Table 1: American Society of Anesthesiologists Physical Status Classification

ASA I	Normal healthy patients.
ASA II	Patient with mild systemic disease.
ASA III	Patient with severe systemic disease.
ASA IV	Patient with severe systemic disease that is a constant threat to life.
ASA V	Moribund patient who is not expected to survive without the operation.
ASA VI	Patient declared brain-dead whose organs are being removed for donor purposes.

Table 2: Definition of general anesthesia and levels of sedation/analgesia

	Minimal sedation (anxiolysis)	Moderate sedation/ analgesia (conscious sedation)	Deep sedation/ analgesia	General anesthesia
Responsiveness	Normal response to verbal stimulation.	Purposeful response to verbal or tactile stimulation.	Purposeful response following repeated or painful stimulation.	Not arousable, even with painful stimulus.
Airway	Unaffected.	No intervention required.	Intervention may be required.	Intervention often required.
Spontaneous ventilation	Unaffected.	Adequate.	May be inadequate.	Frequently inadequate.
Cardiovascular function	Unaffected.	Usually maintained.	Usually maintained.	May be impaired.

anesthesia.[12] Literature suggests that mild to moderate anxiety should be managed by minimal sedation using oral benzodiazepines,[13] while moderate to severe anxiety should be handled by intravenous, intramuscular or oral benzodiazepines to obtain conscious sedation.[14] Managing the other types of anxiety requires deep or general anesthesia with the ability to maintain ventilatory and cardiovascular functions.

Triazolam

Triazolam is one of the most commonly used pretreatment medications in dentistry. A hypnotic benzodiazepine, it has a very short elimination half-life, reported to vary between 1½ and 5½ hours. Triazolam is considered an intermediate-onset-of-action medication, with a peak onset that ranges from 45 minutes to 2 hours. Triazolam offers ease of use and has no active metabolites to consider for dosing and termination of action.[15]

Although it's a short-acting benzodiazepine, triazolam is considered one of the more potent benzodiazepines. Interestingly, triazolam does not have an established Food and Drug Administration Maximum Recommended Drug (MRD) dosage for unmonitored home use.[16] Triazolam was initially intended for less than 10 days of use to treat insomnia, and is often used for patients with sedation needs scores ranging from 3–6 with short dental procedures.

Triazolam: Dosage and administration mode for dental anxiety[37,38]

Dosage	Administration route	Onset of sedation
0.125–0.5mg	Oral	0.75–2 hours

Midazolam

Midazolam was synthesized for the first time by Fryer and Walser in 1976.[17] It represents a different form of benzodiazepines than triazolam and quickly gained popularity for sedation. Midazolam offers a more pronounced amnestic effect than other benzodiazepines, and has a rapid onset and short duration of action. The stability of midazolam allows it to be prepared and easily administered orally, intranasally, intramuscularly and intravenously. Oral and intranasal dosing of midazolam is typically provided to the pediatric population in dentistry and for patients less than 40 kilograms; therefore, those routes will not be covered here.

Intramuscular (IM) and intravenous (IV) administration of midazolam can provide sedation with a hypnotic-like effect for dental procedures. The onset of action of the IM route is approximately 15 minutes with a peak effect occurring in 30–60 minutes. The IV route onset of action ranges from 3 to 6 minutes. The onset of action for IV sedation is both dose-dependent and dependent on concurrent opioid medication administration. Caution and appropriate patient monitoring are key factors in sedation safety with the administration of midazolam because of its ability to induce anesthesia and result in respiratory compromise. Dental practitioners are encouraged to refamiliarize themselves with the FDA monograph on midazolam administration because of safety considerations.[18]

Dental providers should consider that midazolam is short-acting and considered three to four times more potent than diazepam. The manufacturer's drug monograph states that dosing of midazolam should not be based solely on the pharmacokinetics of the medication but rather on the clinical effects.

The FDA monograph for MRDs for IM and IV dosing provide ranges for ASA I and II patients who are 60 or younger without significant comorbidities. IM midazolam MRDs are 0.07–0.08mg/kg and the IV MRDs range from 1–2.5mg with conservative administration and patient monitoring. Maintenance dosages of IV midazolam are recommended to be 25% or less of the initial dose.[18] Literature suggests that patients well-suited for the administration of midazolam have sedation needs scores of 5–6.

Midazolam: Dosage and administration mode for dental anxiety[23–25]

Dosage	Administration route	Onset of sedation
0.5mg/kg	Intramuscular	15 minutes
1mg/2min	Intravenous	3–6 minutes

Lorazepam

Lorazepam is considered a highly potent and long-acting benzodiazepine. Lorazepam, like other benzodiazepines, produces a hypnotic-like effect and some amnesia. It has an intermediate onset of action.

Reviewing the half-life of lorazepam, one recognizes the half-life is much shorter than the sedation effects this medication exerts. Lorazepam's lower lipid solubility and its propensity to be less bound to plasma proteins increases the duration of its sedation of effects. Therefore, lorazepam is less affected by variables such as poor nutritional status, advanced age and hepatic dysfunction. Its potency and long duration of action cause the practitioner to carefully consider appropriate patient selection and length of dental procedure when utilizing this benzodiazepine.

The FDA monograph MRD for unmonitored home use is 2–6mg/day.[19] However, dental literature recommends a usual dose of 2–3mg total for dental procedures.[15] Lorazepam may be best utilized in patients with sedation needs scores ranging from 3–6, an ASA I or II classification and for moderate duration to longer dental procedures.

Lorazepam: Dosage and administration mode for dental anxiety[22–24]

Dosage	Administration route	Onset of sedation
2–3mg	Oral	1 hour. Sedation effects: 6–8 hours

Diazepam

Diazepam is the benzodiazepine with the longest half-life, the range of which may be attributed to metabolites, the strong binding to plasma proteins, the dosage administered and the route of administration.

Diazepam, like lorazepam, is also available in multiple forms of administration; we will review only the oral route of administration. Oral diazepam is useful for sedation with its low potency, rapid onset and long duration of action properties. With its long half-life, diazepam is a good choice for anxiolysis, given the night before dental procedures or for longer dental procedures. It is usually best utilized for longer procedures scheduled earlier in the day to allow the medication to exert its effects and to permit safe recovery and discharge of the patient. As with lorazepam, there are varying reports of MRDs. The FDA monograph for oral diazepam recommends caution, with the recommended dosages for unmonitored home use ranging from 2–10mg up to four times a day in certain circumstances. The FDA stresses that dosages should be individualized to the patient.[20] Dental literature has reported the average adult dose for dental procedures is 5mg with some sources citing a maximum dose of 20mg.[22–24] Diazepam can be considered beneficial in patients who score 3–6 on their sedation needs scoring, are an ASA I or II and have lengthier dental procedures.

Diazepam: Dosage and administration mode for dental anxiety[25,26]

Dosage	Administration route	Onset of sedation
2–20mg	Oral	1 hour

Best practices when administering benzodiazepines for dental procedures

There are many considerations when evaluating a patient for dental sedation. Appropriate patient selection, availability of appropriate monitors, availability of appropriately trained staff and medication selection are all key components to provide safe passage through dental care. Here are some key points to consider when providing anxiolysis with benzodiazepines:[15]

- Obtain a thorough medical and medication history.
- Assess the patient's baseline anxiety/dental phobia(s).
- Appropriately classify patients with ASA classification.
- For first time anxiolysis treatment, schedule early morning, short procedures.
- Ensure there is a designated driver.
- Preprocedure: Obtain baseline vital signs.
- Document the time the medication was administered, the dosage that was specific for your patient and the patient's response to the dosing.
- Postprocedure: Obtain vital signs, document the state of the patient, the time of dismissal and the receipt of discharge instructions.

Contraindications and special considerations

There are special considerations and potential contraindications to any medication that is administered; the same holds true for benzodiazepines. For all medications, administration should be avoided for any known allergy to the medication, one of its components or metabolites.

Benzodiazepines work in the central nervous system. It's prudent to avoid compounding CNS depression with the concomitant use of narcotic pain medications, antihistamines and the acute ingestion of alcohol. This class of medications may have prolonged effects in the geriatric and medically compromised populations. Caution must be exercised in these populations and those with impaired kidney or liver functions.

There are certain disease processes that warrant avoiding specific benzodiazepines, including triazolam and diazepam. Both triazolam and diazepam are contraindicated in acute narrow-angle glaucoma. Triazolam is contraindicated in the neurological disease myasthenia gravis.[15]

Reversal of benzodiazepines with flumazenil

The greatest variable in sedation dentistry is the patient. Although great care is provided in appropriate patient and medication selection, unintended overdose may occur. Any administration of a sedative warrants that the practitioner is prepared to treat an unintended overdose. The FDA monographs for each of the benzodiazepines discussed advocates for appropriate patient monitoring, airway management and the potential administration of a benzodiazepine-receptor antagonist such as flumazenil. This reversal agent provides partial or complete reversal of the sedative effects of benzodiazepines.

Reversal of benzodiazepines with flumazenil can be achieved via the IV route. It is the only route of administration, according to the FDA monograph. The typical vial of flumazenil contains 5ml in a concentration of 0.1mg/ml. The initial dose of flumazenil is 0.2mg given over 15 seconds. The dose of flumazenil may be repeated after 45 seconds. Subsequent doses of 0.2mg may be repeated up to the maximum recommended dosage of 1mg. Dosage of 0.1–0.2mg provides partial benzodiazepine reversal; increasing dosage gives complete reversal. The peak effect of flumazenil is 6–10 minutes.[21]

Resedation may occur after the administration of flumazenil, depending on the sedation duration and the half-life of the specific benzodiazepine that was administered. The half-life of flumazenil is 54 minutes. It is plausible that active components of benzodiazepines may still be in a patient's system when the effects of flumazenil have worn off. This allows the

benzodiazepine to re-exert its sedation effects. This is important in considering the safe discharge of a patient. The patient should not be discharged until it has been determined that the potential for resedation and compromise no longer present a potential threat to the patient. ■

Flumazenil: Dosage and administration mode for benzodiazepine reversal

Dosage	Administration route	Half-life
0.2mgx	Intravenous	54 minutes

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1. Studies have shown that _____% of Americans never or rarely visit the dentist due to their dental phobia/anxiety.

A. 1–3.
B. 5–7.
C. 8–10.
D. 11–15.

2. Benzodiazepines exhibit all of the following properties except:

A. Antianxiety.
B. Sedative–hypnotic.
C. Seizure inducer.
D. Skeletal muscle–relaxant.

3. True or false: Benzodiazepines exert their effects in the central nervous system.

A. True.
B. False.

4. Dose reduction strategies should be considered when treating the following patient populations:

A. Advanced age.
B. Poor nutritional status.
C. Liver insufficiency.
D. All of the above.

5. An Indicator of Sedation Needs final score of _____ indicates a moderate need for sedation.

A. 3–4.
B. 5–6.
C. 7–9.
D. 10–12.

6. With anxiolysis, the following systems are unaffected by the effects of benzodiazepines except:

A. Skeletal muscle system.
B. The ability to breathe independently.
C. Airway patency.
D. Cardiovascular function.

7. True or false: Midazolam is long-acting when injected intravenously.

A. True.
B. False.

8. Which of the following are true of diazepam?

A. Peak plasma concentrations occur within 10 minutes of administration.
B. Exhibits poor plasma protein binding.
C. The active metabolite lasts 20–30 hours.
D. The acute half-life is 6–8 hours.

9. True or false: Triazolam is the shortest-acting benzodiazepine discussed in the article.

A. True.
B. False.

10. The duration of action of triazolam is between _____ hours.

A. 0.5–1.0.
B. 1.0–1.5.
C. 1.5–2.0.
D. 2.5–3.0.

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Common Benzodiazepines

by Tammy Smit, CRNA

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