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Comparison of Triazolam and Zaleplon for Sedation of Dental Patients

Dennis Flanagan, DDS, and Jason H. Goodchild, DMD

Dental patient anxiety can hinder, delay, or prevent treatment. An anxious patient can be difficult to treat and may not respond as well to treatment as an unafraid, relaxed patient. It may be necessary to administer sedative medications to some dental patients to allow treatment to occur.^{1,2} Many medications are available to the dentist that will provide sedation during dental treatment. Ideally, the patient who requires sedation for a short dental procedure (30 to 90 minutes) should be treated with a drug that provides sedation for this period and loses its effect very soon thereafter. Two drugs that may satisfy this requirement are triazolam (Halcion, Pfizer) and zaleplon (Sonata, Wyeth Laboratories). In this article triazolam and zaleplon are compared with an emphasis on their utility as sedatives during dental treatment (Table 1).

	Triazolam	Zaleplon
Agents and Dosages	0.125- and 0.5-mg tablets	5- and 10-mg capsules
Onset of Hypnotic Effect	15 to 30 minutes	15 to 30 minutes
Serum Half-Life	1.5 to 5.5 hours	1 hour
Peak Time	2 hours	1 hour
Risk of Adverse Effects	low with a single dose not over 0.5 mg	low ³ although not well-studied, dose over 20 mg is not recommended
Drug Interactions That Increase Effect	other sedatives, ethanol, macrolides, cimetidine, some calcium channel blockers, ketoconazole, itraconazole	other sedatives, ethanol, imiprimine, thioridazine, cimetidine, erythromycin, ketoconazole, many drugs have been not studied
Foods That May Increase Effect	grapefruit, star fruit, ethanol, kava, valerian, melatonin, chamomile	ethanol
Drugs That Decrease Effect	rifampin, phenytoin, carbamazepine, some calcium channel blockers	phenytoin, carbamazepine, phenobarbital, rifampin
Foods That May Decrease Effect	St. John's Wort	high-fat meal
Relative and Absolute Contraindications	hypersensitivity, COPD, depression, pregnancy, lactation, myesthesia	hypersensitivity, pregnancy, liver impairment, severe renal disease, children
Bioavailability	50%	30%
Cost (average wholesale price)	0.25 mg: \$1.53 (Halcion), 0.25 mg: \$0.14 (generic)	10 mg: \$3.18 (Sonata)

Triazolam

Triazolam is a short-acting benzodiazepine sedative/hypnotic usually active for less than 6 hours.³ It is a member of the same drug class

as diazepam, midazolam, and lorazepam. Triazolam is used for conscious sedation in the dental setting, for the short-term treatment of insomnia, and for individuals experiencing jet lag. It is a Controlled Substances Act Schedule IV drug with a low to moderate risk for dependence. The usual sedative dose is 0.125 mg or 0.25 mg per os (given orally). This drug is not available in an intravenous or intramuscular form.

Triazolam depresses all levels of the neuroaxis by inhibiting neurotransmitter receptors directly activated by the amino acid gamma-aminobutyric acid (GABA).⁴ It is not routinely dosed according to body weight calculations; instead, triazolam is given empirically as a 0.125- or 0.25-mg dose. The average effective dose is 0.25 mg; however, 0.125 mg is recommended for the elderly, patients with complex medical histories, and individuals of small body size. To minimize the risk of adverse reactions, the total dose of triazolam should not exceed 0.5 mg at any single administration.

Intestinal and microsomal liver enzymes metabolize triazolam. The cytochrome P450 enzyme family is the major catalyst for drug biotransformation. There are 12 subgroups, the most predominant of which is CYP3A. Triazolam is metabolized initially by hydroxy-lyation catalysis by CYP3A and is highly dependent on this enzyme for clearance. The parent compound is converted into alpha-hydroxytriazolam, an active metabolite that is rapidly conjugated with glucuronic acid, preventing any appreciable residual clinical effect. The inactive conjugated glucuronide metabolites are excreted in the urine, and a small amount of nonmetabolized drug is also excreted.^{4,5} Severe liver dysfunction will result in reduced metabolism of triazolam, potentially increasing its plasma concentration. The plasma elimination half-life is 1.5 to 5.5 hours and peaks (1 to 6 ng/mL) within 2 hours of oral administration.^{4,5}

Drugs and chemicals that affect the CYP3A enzyme can alter the clinical effects of triazolam. Macrolide antibiotics such as erythromycin and clarithromycin, and cimetidine (a medication for the treatment of duodenal and gastric ulcers) may cause increased plasma levels and therefore an increase in the clinical effects of triazolam. Nelfinavir and ritonavir, viral protease inhibitors used in the treatment of human immunodeficiency virus, impair the clearance of triazolam and increase its clinical effects, including respiratory depression.⁶⁻⁸ Antifungal agents such as ketoconazole and itraconazole prolong the duration of many benzodiazepines, including triazolam. The calcium channel blocker mibefradil is a potent inhibitor of CYP3A⁴, causing an increase in plasma triazolam levels. Other calcium channel blockers have variable effects on the metabolism of triazolam.^{9,10} In contrast, oral contraceptives, proton pump inhibitors, and ranitidine may cause an increased effect of triazolam, although this effect may not be related to CYP3A inhibition.¹¹ The antituberculosis antibiotic rifampin and the anticonvulsants carbamazepine and phenytoin increase the metabolism of benzodiazepines by enzyme induction, thus reducing their effects.⁵

Use of triazolam can affect fetal development, especially in the first trimester. The drug passes through the placental barrier and has been implicated in the development of congenital malformations. It is contraindicated in pregnancy and is classified as a category X drug where studies have demonstrated fetal abnormalities or there is evidence of fetal risk that outweighs any benefit.^{12,13} It is not recommended for use by nursing mothers due to its accumulation in breast milk.¹³

Some tropical fruits and juices (eg, grapefruits, tangerines, limes) have been shown to affect the metabolism of medications. Many benzodiazepines exhibit increased plasma levels after ingestion of fruits such as grapefruits, limes, or star fruit.^{14,15} The inhibition may affect the enteric but not the hepatic CYP3A enzymatic activity and may not recover for 2 to 3 days.¹⁶ Grapefruit juice can cause a 25% increase in the plasma concentration of triazolam.¹³ Some herbals with a sedative effect, such as kava, chamomile, valerian, and melatonin, may add to the sedation effect of triazolam. Because there have been few studies of herbal drug interaction, caution is recommended when administering herbal sedatives concomitantly with triazolam.¹⁷

Further, erythromycin produces a 46% increase in plasma concentration of triazolam.¹³

At doses used for sedation, benzodiazepines do not generally affect respiration in healthy patients. In fact, a study by Skatrud found that 2 to 4 mg of triazolam did not depress cardiac or respiratory dynamics.⁶ In very high doses, however, this drug can cause a reduction of the hypoxic drive, leading to respiratory acidosis. In patients with chronic obstructive pulmonary disease, triazolam can induce hypoxia or carbon dioxide narcosis. Sleep apnea is a contraindication for triazolam sedation; it may increase the severity of apneic episodes, causing hypoxia, pulmonary hypertension, and increased cardiac ventricular load.⁴

Triazolam causes anterograde amnesia. The sedated patient may have no or only limited memory of the dental procedure. For some dental patients, little memory of dental treatment is desirable, while others regard it as troubling. A patient who feels a loss of control may have increased fear and anxiety.¹⁸ Further, the use of triazolam in children is not approved by the FDA but has been studied in this cohort.¹⁹⁻²¹

The additive sedative effects of ethanol and triazolam may cause serious oversedation, CNS depression, and death.²² Patients should be counseled to avoid alcohol during triazolam use. Cognitive dysfunction can occur with triazolam without sedation and can persist for up to 6 hours.^{23,24} Driving a car and other such activities should be postponed until the day following sedation.

Manifestations of triazolam overdose are somnolence, confusion, impaired coordination, slurred speech, seizure, and coma.²⁵ An overdose of triazolam is treated with flumazenil (Romazicon, Roche Laboratories). Triazolam is antagonized by this drug, which is a benzodiazepine congener that acts by selectively blocking the benzodiazepine binding sites in the central nervous system and thus ameliorating the effects. Although flumazenil is approved for intravenous administration, other routes such as sublingual, submucosal, and intranasal have been studied.²⁶⁻²⁸ Other steps in the treatment of an overdose include: monitoring vital signs, gastric lavage, airway maintenance, and the administration of intravenous fluids. If flumazenil is used, it must be incrementally administered via the intravenous route in 0.2-mg doses over 2 to 3 minutes until the signs of overdose cease. If the patient does not respond with a cumulative dose of 1 to 5 mg, then the overdose is not the result of a benzodiazepine. Flumazenil is not effective when the overdose is due to barbiturates, tricyclic antidepressants, or ethanol.

Sublingual administration of triazolam can be advantageous for the dentist. This route of administration avoids some first-pass metabolism and can produce a greater anxiolytic effect without an increase in side effects.²⁹ For more effective and immediate results patients can be

instructed to take 0.25 mg sublingually at bedtime the evening before the dental procedure and again 1 to 2 hours before the appointment. The patient must be driven to and from the office and be admonished from driving a car or operating equipment on the day of administration. The patient should be asked by the dentist about symptoms of weakness, headache, blurred vision, vertigo, nausea, vomiting, epigastric distress, diarrhea, joint pain, chest pain, or incontinence. These may be the symptoms of impending overdose or sensitivity.

Zaleplon

Zaleplon is a sedative in the pyrazolopyrimidine class, and its chemical structure is not related to the benzodiazepines, barbiturates, or other hypnotics.³⁰ It was approved for sale in the United States in August of 1999. Zaleplon is supplied in 5- and 10-mg capsules. The usual dose for oral conscious sedation is 10 mg, but the lower 5-mg dose may be used in persons of low body weight, the elderly, or patients with hepatic or renal impairment. Dosages in excess of 20 mg are not recommended.

Similar to the benzodiazepines, zaleplon acts on the gamma-aminobutyric acid (GABA) receptor. Specifically, there is evidence that it preferentially binds to omega-1 receptors on the alpha subunit of the GABA A receptor complex in the brain. This is believed to give zaleplon its sedative properties. It is chemically and pharmacologically related to zolpidem (Ambien) and zopiclone (Imo-vane).³¹

Zaleplon is lipophilic and is rapidly absorbed, with peak plasma concentrations being achieved about 1 hour after oral administration. The drug undergoes extensive first-pass metabolism with an oral bioavailability of about 30%

of the administered dose. Zaleplon is metabolized by the liver with less than 1% excreted unchanged in the urine. It is distributed evenly throughout the blood volume with substantial distribution into extravascular tissue. Zaleplon is primarily changed to 5-oxo-zaleplon by aldehyde oxidase with a smaller percentage metabolized by cytochrome P450 (CYP) 3A4 into desethylzaleplon and 5-oxo-desethylzaleplon. These oxidized entities are changed into glucuronides and excreted via the urine.³² None of these metabolites are pharmacologically active.

The plasma elimination half-life of zaleplon is one hour. Approximately 70% of metabolized zaleplon is found in the urine and 17% in the feces. Zaleplon is a preferred dental sedative because of its rapid elimination and low incidence of residual side effects after a single dose. Despite relatively low oral bioavailability and significant presystemic metabolism, a 10-mg dose is effective due to zaleplon's high potency.³³

Zaleplon is contraindicated in patients with known hypersensitivity to this drug. It should be used with caution in patients with depression. The effects may be increased with ethanol or other central nervous system depressants such as imiprimine and thioridazine. Because of high lipophilicity, a high-fat meal taken with or just before oral zaleplon administration prolongs absorption and, compared to fasting intake, can cause a 35% reduction in plasma concentration and a subsequent reduction of its effect.

The dose of zaleplon should be reduced to 5 mg in patients with mild to moderate hepatic impairment. Patients with severe liver impairment should not be treated with zaleplon. Orally administered clearance was reduced by 70% to 87% in cirrhotic patients, leading to marked increased drug availability.³⁰ Zaleplon has not been well-studied in patients with renal impairment. Even though only 1% of zaleplon is excreted in the urine unchanged, it should not be administered to patients with severe renal disease.

Zaleplon is classified as a Schedule IV drug and carries Risk Factor C in pregnancy use. The drug should not be used in pregnant women without consideration of the potential risk to the fetus. Its use in children is contraindicated because safety has not been established.

Inhibitors of aldehyde oxidase and CYP3A4 enzymes may prolong the effects of zaleplon. Drugs that enhance CYP3A4, such as phenytoin, carbamazepine, phenobarbital, and rifampin, may reduce its effect or make it ineffective. Co-administration with erythromycin or ketoconazole, drugs that inhibit CYP3A4, can produce a 34% increase in plasma concentrations of zaleplon.³⁰ Cimetidine inhibits CYP3A4 and aldehyde oxidase, and can produce an 85% increase in the plasma concentration of zaleplon.

The risk of traffic accidents increases when sedatives with longer half-lives are used.³⁴ Four hours after zaleplon administration, the ability of an individual to drive an automobile is unaffected.³⁵ However, the drug can still have a negative effect on the patient's memory.³⁶ Zaleplon is prescribed for the short-term treatment of insomnia. As with all hypnotics, it should be limited to 7 to 10 days of use.³⁷⁻⁴⁰

Protocols

Table 2. Suggested Protocol for Use of Triazolam or Zaleplon for Premedication of Anxious or Fearful Dental Patients.

- (1) Patient must be evaluated for appropriateness of oral sedation. This includes a complete medical history, researching of all potential drug interactions, consultation with the patient's physician if applicable, and informed consent. The extent of dental treatment should be determined.
- (2) A responsible adult companion is identified for travel to and from the dental office on the day of sedation.
- (3) The patient takes the prescribed dose of triazolam or zaleplon 30 to 60 minutes before the dental treatment is to begin. Patients are instructed not to eat or drink (with the exception of water) for 6 hours before sedation.
- (4) After taking the medication, while in the office, the patient is monitored both visually and with a pulse oximeter. Patients who have received oral medications are never left alone.

- (5) After the treatment is complete, patients are given 6 oz of carbohydrate-rich drink to begin the recovery process.
- (6) All postoperative instructions are given to both patient and companion.
- (7) After the discharge criteria are met, the patient is released into the care of his or her companion for travel home. Once home, the companion is instructed to call the dental office to confirm arrival.
- (8) The patient is scheduled for a follow-up visit within 7 days.

Both triazolam and zaleplon are suitable for use as premedication of anxious or fearful dental patients. In either case, the recommended protocol for use is the same. The difference between triazolam and zaleplon is in the amount of anticipated treatment time—2 hours and 1 hour, respectively. The protocol for oral sedation with either drug is described in Table 2. Nitrous oxide/oxygen analgesia can be used in conjunction with either drug.

Preoperatively, all potential oral sedation patients must undergo a thorough evaluation of their medical history and medical status. This evaluation includes assessment of potential drug interactions, a consult with the patient's physician, and informed consent for all planned procedures. Because all patients, regardless of medication used, must be driven to and from the office for the sedation visit, a responsible adult companion must be identified for travel. Postoperatively, all patients must satisfy discharge criteria before being dismissed from the dental office. Criteria for dismissal may include factors such as patient orientation to time/place/location, alertness, ability to ambulate, and adequacy of verbal responses.⁴¹

Legal Issues

Recently, oral sedation in dentistry has garnered significant attention from regulatory agencies. Although oral premedication for the reduction of anxiety/fear is not a new practice in dentistry, in recent years the technique has become popular and widespread. The American Dental Association (ADA) published a policy statement on the "use of conscious sedation, deep sedation, and general anesthesia in dentistry" in 1999, recognizing that pharmacological approaches to anxiety may be required for some patients.⁴² The policy statement states, "The use of anxiolytic sedative and anesthetic techniques by appropriately trained dentists in the dental office and other settings continues to have a remarkable record of safety."

The ADA has also published guidelines for the use and teaching of sedation in the dental office (published in October 2003).⁴³ This topic is outside the scope of this article; triazolam and zaleplon as described in this paper are recommended for use by a single administration 30 to 60 minutes before a planned dental procedure. Note that each state dental board has the purview of establishing laws or regulations for the provision of in-office oral sedation. The ADA's recommended requirements for teaching oral conscious sedation include 18 didactic hours of training and 20 clinically oriented experiences.⁴³ Currently, 10 states have requirements that match the ADA recommendations, with 8 additional states in the process of enacting consonant requirements. Wide variability exists between state regulations. Thirteen states have no requirements for the use of oral conscious sedation, and another 12 do not separate oral from intravenous conscious sedation and satisfy the requirements for the latter (60 hrs didactic plus treatment of 20 patients).⁴⁴

Conclusion

Both triazolam and zaleplon are short-acting sedatives that are safe for use at the recommended doses described. Zaleplon is a newer drug (1999) and has not been as well-studied as triazolam. A summary of the characteristics of each drug is presented in Table 1. The risks of adverse effects are low with recommended use. Neither drug has clinically significant active metabolites. The effects of triazolam and zaleplon can be modified with concomitant use of other drugs, foods, or herbals. The practical use of one drug over the other may be based on the length of the procedure or appointment. Triazolam may be more suitable for appointments lasting up to 2 hours, whereas zaleplon may be better suited for use in short appointments lasting up to 1 hour.

A modification of the protocol listed in Table 2 is to dose the patient at bedtime the evening before the appointment, followed by another dose 1 hour before the scheduled appointment. The patient is always driven to and from the appointment.

Since there have been no kinetic studies examining multiple incremental (titration) use of these drugs, caution should be observed if additional intraoperative doses are required.

Dentists should review the ADA's recommended requirements for teaching oral conscious sedation as well as their own state dental board's requirements.

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Dr. Flanagan is a general dentist in Groton and Willimantic, Conn. He is board certified by the American Board of General Dentistry and the American Board of Oral Implantology/Implant Dentistry. He can be reached at (860) 456-3153 or dfdds@charter.net.

Dr. Goodchild is assistant professor and director of oral diagnosis in the department of diagnostic sciences of the New Jersey Dental School, and a clinical assistant professor in the department of oral medicine at the University of Pennsylvania School of Dental Medicine. He can be reached at (973) 972-9431 or goodchjh@umdnj.edu.

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Continuing Education Test No. 69.1



After reading this article, the individual will learn:

• to understand the metabolism of orally administered triazolam and zaleplon, and
• to understand the differences and appropriate use of triazolam and zaleplon.

1. Triazolam is not _____.

- a. a Controlled Substances Act Schedule V drug
- b. used for the treatment of jet lag
- c. a benzodiazepine
- d. administered intravenously

2. Zaleplon is not _____.

- a. a pyrazolopyrimidine
- b. a benzodiazepine
- c. lipophilic
- d. metabolized to 5-oxo-zaleplon

3. Triazolam can be used in patients _____.

- a. who are pregnant
- b. with severe liver disease
- c. with moderate liver disease
- d. with sleep apnea

4. The plasma elimination half-life of triazolam is _____.

- a. 0.5 to 1 hour
- b. 0.5 to 1.5 hours
- c. 1.5 to 5.5 hours
- d. 5.0 to 8.0 hours

5. Triazolam is not _____.

- a. initially hydrolysed by hydroxylation
- b. metabolized by monochrome P550 3B
- c. changed into clinically active metabolites
- d. given in a 0.125- to 0.25-mg dose

6. Grapefruit juice _____.

- a. affects benzodiazepine metabolism
- b. enhances enteric CYP3A4 enzymes
- c. can cause a 90% increase of plasma concentration of triazolam
- d. all of the above

7. An overdose of triazolam is treated with intravenous _____.

- a. ethanol
- b. flumazenil
- c. diazepam
- d. zaleplon

8. The most advantageous route of administration for triazolam when used as part of dental treatment may be _____.

- a. sublingually
- b. orally
- c. intravenously
- d. parenterally

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