ORAL TRIAZOLAM SEDATION IN IMPLANT DENTISTRY

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KEY WORDS

Triazolam
Sedation
Contraindications
Flumazenil

Triazolam can be helpful for sedating dental implant patients when administered orally or sublingually in low dosages of 0.125 or 0.25 mg, but not exceeding 0.5 mg. It is a fast- but short-acting benzodiazepine with few side effects, and it has a long record of successful use. Its effects can be reversed with incremental intravenous flumazenil, although there is a risk of seizure. Triazolam has not been shown to be carcinogenic, and it has a low potential for abuse and addiction. It is contraindicated in patients who are pregnant, breast-feeding, and those concomitantly taking ethanol, macrolid antibiotics, some protease inhibitors, psychotropic medications, ketoconazole, itraconazole, nefaxodone, or other medications that impair oxidative metabolism mediated by cytochrome P450 3A (CYP 3A). Triazolam should be used with caution in patients taking grapefruit juice, cyclosporine, and other drugs such as calcium channel blockers including nifedipine, verapamil, and diltiazem. The lowest effective dose should be used.

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INTRODUCTION

Some dental implant patients may require sedation because of previous adverse experience or ideation. Oral sedation may be a safe and effective method to make the procedure much more tolerable for the patient and to ensure a favorable treatment outcome without serious morbidity. A surgical implant placement may require several hours of appointment time. Before and during this time some patients may be very fearful or extremely anxious. Pre-operatively they may develop anxieties that hinder the procedure or the post-operative course. Triazolam (Halcion, Pharmacia/Pfizer, Kalamazoo, Mich), because of its short duration of action, ease of use, and safety may be one of the most suitable medications for in-office dental implant surgery.[1,2] In-office sedation with triazolam may be done per os or sublingually.

PHARMACOLOGIC AND CHEMICAL PROPERTIES

Triazolam is a short-acting (active for less than 6 hours), benzodiazepine hypnotic, chemically related to diazepam (Valium, Roche Laboratories, Nutley, NJ) and midazolam (Versed, Roche Laboratories, Nutley, NJ) (Figure).

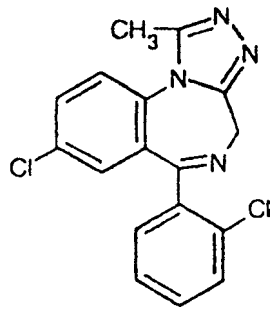

FIGURE. Chemical structure of triazolam.

It is used for sedation, short-term (no more than 7–10 days) treatment of insomnia, and "jet lag." As a benzodiazepine, triazolam is classified as a Schedule IV drug under the Controlled Substances Act, indicating a low abuse potential with a limited or moderate risk for dependence. However, this low abuse potential should not be overlooked. The usual hypnotic dose is a 0.125 or 0.25 mg tablet, the higher dose being the most frequently used. An oral dose calculated by body weight is not the usual course of administration. A 0.25 mg dose is usually effective. The lower 0.125 dose may be sufficient, however, for people who maintain lower body weight and for the elderly. In any case, an oral dose of 0.5 mg should not be exceeded because of the risk of several adverse reactions. Triazolam is not available for intravenous use.

Triazolam acts by depressing all levels of the neuraxis, including the limbic and reticular formation, by inhibiting neurotransmitter receptors directly activated by the amino acid gamma-aminobutyric acid.[3]

Triazolam is metabolized by microsomal liver enzymes and may not induce synthesis of enzymes that may increase metabolism of benzodiazepines or other substances. Initially it is converted to an active compound, alpha-hydroxytriazolam, but this is rapidly conjugated with glucuronic acid, disallowing appreciable accumulation of this active metabolite.[3] Its plasma half-life is 1.5 to 5.5 hours and peaks within 2 hours after oral administration to 1–6 ng/mL. Its metabolites are primarily excreted in the urine, and only a small percentage of unchanged triazolam appears there.[4]

In an electroencephalogram, triazolam produces a decrease in alpha wave activity, which indicates inattention and relaxation. It has a short-term, blood plasma half-life of 1.5 to 5.5 hours. It does not affect prothrombin times or warfarin levels. Its extended use may bring on tolerance. It does apparently cross the placenta, being a potential risk to a fetus, and it is contraindicated in pregnant patients (Category X).[5,6]

Macrolide antibiotics (such as erythromycin and azithromycin), cimetidine (treatment for gastric and duodenal ulcers), and grapefruit juice may cause increased plasma concentration and, therefore, increased clinical effects of triazolam. Concomitant erythromycin produced a 46% increased plasma level, whereas concomitant grapefruit juice produced a 26% increase of plasma-level concentration.[6]

Triazolam is antagonized by flumazenil, a benzodiazepine congener that acts by selectively blocking binding sites and the biological effects of triazolam.

Benzodiazepines, in general, do not affect respiration in healthy patients when used for sedation. A single dose of triazolam is unlikely to produce respiratory distress in dental patients. In safety studies, a high dose of 2 to 4 mg did not depress respiratory or cardiac dynamics.[2(pp134,229)] However, very high doses can depress respirations and produce respiratory acidosis because of a reduction of the hypoxic drive. An overdose can result in death.[4] These effects may be increased in patients with chronic obstructive pulmonary disease and may produce hypoxia or carbon dioxide narcosis. Obstructive sleep apnea is considered by some physicians to be a contraindication for using a sedative such as triazolam because it may increase the brunt of apneic episodes resulting in hypoxia, pulmonary hypertension, and cardiac ventricular load.[3]

Benzodiazepines can produce a minor decrease in blood pressure and a minor increase in heart rate.[3] Triazolam does have an amnesic effect, so that the patient may have no or limited memory of the procedure undergone.[4] Contraindications for its use are: hypersensitivity to triazolam or any component; cross sensitivity with other benzodiazepines; severe, uncontrolled pain; pre-existing central nervous system depression; narrow-angle glaucoma; pregnancy, and breast-feeding mothers.[5]

Triazolam is metabolized initially by hydroxylation catalysis by cytochrome P450 3A (CYP 3A) and may be completely dependent on it for clearance. Various medications and chemicals can affect the enzyme to inhibit or enhance its activity. Nelfinavir and ritonavir, viral protease inhibitors used in HIV treatment, impair the clearance of triazolam and increase its clinical effects, including respiratory depression.[7,8]

Ketoconazole and itraconazole prolong the duration and effects of triazolam and other benzodiazopines (Table). Rifampin (an antibiotic for nonviral infections, such as tuberculosis), carbamazepine (an anticonvulsant), and phenytoin (an anticon-

TABLE 1
Medications, herbals, and food that may affect triazolam use

Contraindications for Use of Triazolam	May Cause Increased Effects of Triazolam	May Cause Decreased Effects of Triazolam
Pregnancy	Macrolide antibiotics	Rifampin
Lactation	Cimetidine	Carbamazepine
Hypersensitivity	Grapefruit juice	Phenytoin
Severe, uncontrolled pain	Benzodiazepines	Rifabutin
Pre-existing depression	Ethanol	
Narrow-angle glaucoma	Mibefradil	
Obstructive sleep apnea	Some calcium channel blockers	
Ethanol	Ranitidine	
Macrolide antibiotics	Fluvoxamine	
Psychotropics	Ciprofloxin	
Ritonavir	Selective serotonin reuptake inhibitors	
Amprenavir	Cyclosporine	
Nelfinavir	Clozapine	
Ketoconazole	CNS depressants	
Itraconazole	Disulfiram	
Nefazodone	Digoxin	
	Fluconazole	
	Fluoxetine	
	Herbal kava	
	Herbal valerian	
	Isoniazid	
	Labetalol	
	Levodopa	
	Metoprolol	
	Metronidazole	
	Nefazodone	
	Omeprazole	
	Phenytoin	
	Rifabutin	
	Rifampin	
	Valproic acid	

vulsant and cardiac antiarrhythmic) reduce therapeutic efficacy of benzodiazepines by inducing their metabolism.[9] Mibefradil, a calcium channel blocker, is a potent inhibitor of CYP3A4, causing an increase of plasma concentration of triazolam; however, another calcium channel blocker, isradipine, does not have this effect.[10] Other types of calcium channel blockers may have varying degrees of influence on triazolam.[11]

Triazolam's use in the treatment of children under age 16 has not been established, and implant treatment in these patients is unlikely and may be contraindicated.[12]

Ethanol and triazolam may produce their sedative effects by the same mechanism and can have additive effects that can lead to death.[13] Triazolam may cause cognitive dysfunction without sedation, and this effect can persist for 6 hours.[14]

DISCUSSION

In general, for dental procedures, fast-acting, short-duration benzodiazepines with rapid elimination with no active metabolites are the most efficacious.[15] Triazolam may suit these criteria for dental implant surgical patients. A hora somni dose before a procedure and another dose 1 hour before the procedure may provide the best results for dental implant surgery. Triazolam can be administered sublingually, which avoids a first-pass metabolism and produces a greater anxiolytic effect without a detectible increase of side effects or psychomotor impairment as compared to oral administration.[16] Most adverse effects appear with high dosages (0.5–1.5 mg), use in the elderly, or chronic usage with inadequate medical supervision.[2(p134)] Overdose manifestations are somnolence, confusion, impaired coordination, slurred speech, and coma. Occasionally, seizures have been reported with overdose, especially in combination with flumazenil. Death has been reported with triazolam by itself or with other benzodiazepines or ethanol. Death from these combinations may occur with a lower than expected dose.[4]

There is no evidence of carcinogenesis with triazolam.

Herbals that have some sedative effect, such as kava and valerian, may add to the effect of triazolam.

Treatment for overdosage includes monitoring vital signs, gastric lavage, maintaining adequate airway, and administering intravenous fluids. Flumazenil (Romazicon, Roche Laboratories, Nutley, NJ), a specific benzodiazepine receptor antagonist, is indicated for complete or partial reversal of the sedative effects, with the understanding that there is a risk of seizure. To manage excessive somnolence or respiratory depression, an airway must be maintained with oxygen, then flumazenil must be administered in 0.2 mg increments over 1 to 3 minutes until signs and symptoms of overdose cease. If the patient does not respond after a cumulative dose of 1 to 5 mg over 2 to 10 minutes, this strongly suggests that triazolam or a benzodiazepine is not the major cause of the sedation. Flumazenil is not effective for overdosage of barbiturates, tricyclic antidepressants, or ethanol.[2,3]

Because of controversial claims due to reported adverse effects of abnormal behaviors during chronic usage, some clinicians are reluctant to use triazolam. Triazolam was removed from the market in the United Kingdom by regulatory authorities in 1991. Clinical assessments of triazolam in the United States and in the United Kingdom are conflicting, and the regulation of triazolam in the United States is more permissive. Apparently, regulatory trust, selection of technical data, and scientific influences differ between the 2 countries, and conflicts of professional and organizational interests may exist between them.[16] The US Federal Drug Administration has reviewed triazolam and declared it to be safe and effective in low doses of 0.125 and 0.25 mg. Many practitioners believe that the benzodiazepines have an important future in clinical treatments.[18]

The patient can be instructed to take an oral dose at bedtime of the evening before the procedure, then another oral or sublingual dose 1 hour before the procedure. The patient must have a means of getting to the location of the procedure and must be admonished not to drive an automobile or operate any machinery on the day of the dosage. The patient should be advised to immediately report any adverse side effects such as weakness, headache, blurred vision, vertigo, nausea, vomiting, epigastric distress, diarrhea, joint pain, chest pains, and incontinence.

CONCLUSIONS

Triazolam may be a safe and effective medication for sedating dental implant patients in dosages of 0.125 and 0.25 mg, but not exceeding 0.5 mg. Sublingual administration may provide a greater degree of sedation with comparatively less psychomotor impairment. It is contraindicated for patients who are pregnant, breast-feeding or concomitantly taking ethanol, macrolide antibiotics or psychotropic medications, cimetidine, some protease inhibitors, ketoconazole, itraconazole, nefazodone, and any medications that impair oxidative metabolism mediated by cytochrome P450 3A (CYP 3A). It is contraindicated in patients with depression or obstructive sleep apnea. Elderly patients may be susceptible to adverse, dose-related effects and need lower dosages. Oral administration with grapefruit juice may cause increased plasma levels and half-life. Triazolam should be used with caution in patients taking ranitidine, fluvoxamine, nifedipine, diltiazem, verapamil, sertaline, paroxetine, ergotamine, cyclosporine, amidarone, and nicardipine.[4] Rifampin, carbazepine, and phenytoin can cause a loss of efficacy. Flumazenil can be used intravenously, incrementally over 1 to 3 minutes to antagonize triazolam overdose, but there is a risk of seizure. The lowest effective dose of triazolam should be administered.

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