Zaleplon (Sonata) Oral Sedation for Outpatient Third Molar Extraction Surgery

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Zaleplon was compared with triazolam for oral sedation in a third molar surgery model using a double-blind crossover design. Factors such as anxiolysis, amnesia, and quality of sedation were assessed. Of the 14 participants who completed the study, zaleplon sedation was found to be similar to triazolam sedation in all regards except that recovery from zaleplon was more rapid.

Key Words: Zaleplon; Triazolam; Oral sedation; Third molar surgery; Anxiolysis; Amnesia.

Because of the large number of patients who are anxious regarding dental or oral surgical treatment, dentists have developed a range of techniques to provide anxiolysis and/or sedation for procedures that they perform. The most common forms of sedation in the dental office are nitrous oxide–oxygen inhalation sedation, or oral sedation with benzodiazepines.

Triazolam (Halcion), a benzodiazepine derivative, is a sedative-hypnotic drug with a short half-life that causes little residual central nervous system depression (ie, drowsiness or “hangover”). Off label, triazolam has shown great utility as an anxiolytic-sedative for dental procedures. Orally administered triazolam, 0.5 mg, with 50% nitrous oxide in oxygen produces anxiolytic activity during oral surgery, which is comparable, on average, to 19 mg of intravenous diazepam.¹ Peak plasma levels of orally administered triazolam are generally reached within 2 hours after oral administration, with clinical sedative effects realized in as quickly as 30 minutes.² Additionally, triazolam has a short beta half-life, with a reported range of 1.5 to 5.5 hours, with no active metabolites.³ However, common adverse effects of triazo-

lam may be undesirable for some patients. Ordinarily, these are extensions of desirable effects for which the drug was originally prescribed. These adverse effects occur more commonly later in the day after the dental appointment but may extend to the following day and include morning drowsiness, dizziness, nervousness or irritability, and impaired coordination. More serious adverse effects may occur but are more common with repeated doses and accumulation of the drug.⁴ These effects include significant memory impairment, abnormal thinking or behavior, confusion, anxiety, and depression.

Zaleplon (Sonata) is a short-acting, nonbenzodiazepine γ -aminobutyric acid A (GABA_A) agonist hypnotic, which has no active metabolites. It has proven to be effective in the treatment of patients with sleep disorders by presenting less residual central nervous system or “hangover” effects, which are seen in patients using other drugs of the benzodiazepine group.^{5,6} Although not structurally related to the benzodiazepines, zaleplon has many pharmacological characteristics of that class. Differential binding to various GABA_A sites may relate to slightly different clinical effects from benzodiazepines, such as less anxiolysis but more profound hypnosis. The most common current clinical application of Zaleplon is to treat insomnia. This drug has a rapid onset after oral ingestion, with an average onset of activity of 15 to 20 minutes. In addition to rapid absorption, zaleplon has a

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short elimination half-life of approximately 1 hour. The drug is hepatically metabolized, mostly by aldehyde oxidase and to a lesser extent by cytochrome 3A4. Cytochrome 3A4 inhibitors and inducers may affect serum concentrations. For instance, rifampin decreased serum levels by 80%, and cimetidine increased serum levels by 85%. Drowsiness and headache are the most common adverse effects. The approximate duration of action is only 4 hours. Also due to the rapid metabolism of this drug, zaleplon would be expected to have a shorter duration of residual central nervous system depression compared with triazolam. Zaleplon is associated with a lower incidence of adverse effects, such as daytime drowsiness.^{6,7} This study sought to measure the usefulness of zaleplon as an oral premedication for outpatient oral surgical procedures performed with local anesthesia and to compare its antianxiety and amnesic effects with oral triazolam, another oral sedative commonly used in dentistry.

METHODS

After approval from the Ohio State University Human Subjects Review Committee, subjects were sought from those presenting to the Department of Oral and Maxillofacial Surgery, Ohio State University College of Dentistry, who required extraction of 4 impacted third molar teeth with sedation and local anesthesia and who had already consented to the procedure and sedation. Inclusion criteria included patients who had American Society of Anesthesiologists physical status I or II and were between the ages of 18 and 40 years. Exclusion criteria included patients with an American Society of Anesthesiologists physical status of III or higher, prisoners or wards of the state, minors, patients with mental retardation or developmental disabilities, pregnant or breastfeeding patients, patients actively trying to become pregnant, patients with glaucoma, patients who regularly take benzodiazepines or opioids, and patients who were allergic to any drugs used in the study. This was a double-blinded, crossover study in which participants agreed to be present for 2 surgical sedation sessions during which either the right or left third molars were extracted with the patient under oral sedation with either triazolam or zaleplon. Standard preoperative instructions were given. All participants took nothing by mouth after midnight and were scheduled for morning appointments. Unrestricted clear fluids were allowed for all participants up to 2 hours before the procedure. All women were required to undergo a urine pregnancy test to ensure that they were not pregnant.

Participants were randomly assigned to receive one of the study sedative medications, zaleplon, 10 mg, or

triazolam, 0.5 mg, for the first surgery and the other medication on the second surgery. The dosages were both the maximum recommended dosages for nighttime insomnia. Additionally, patients were randomized as to which side of the mouth third molars would be extracted. Although no emergencies were encountered, the clinic nurse was present at all times to reveal which drug was administered in the event of an emergency.

On the day of the surgery, the patient arrived 45 minutes before the procedure, when nothing by mouth status and available escort were confirmed. Individuals were asked to assess their anxiety level using a 100-mm visual analog scale (VAS) with “no anxiety” at the left-hand edge and “extremely anxious” on the right-hand edge. A memory card that depicted a picture of an animal with the name of the animal under the picture was shown to the participant for 10 seconds. At that time, participants received either zaleplon, 10 mg, or triazolam, 0.5 mg, per mouth with a small sip of water. Additionally, rofecoxib (Vioxx), 50 mg, was administered per mouth with a small sip of water. After 45 minutes, participants were escorted into the surgical suite and a similar anxiety scale recorded and different memory card shown for 10 seconds. Patients were monitored via noninvasive blood pressure cuff and pulse oximeter throughout the entire procedure. Initial vital signs and oxygen saturation were recorded. Oxygen was administered by nasal cannula at 3 L/min. Oxygen saturation and heart rate by pulse oximetry were continuously monitored, and blood pressure was assessed every 10 minutes.

Third molar surgery using 2% lidocaine with 1:100,000 epinephrine as local anesthesia was performed in standard fashion following long-standing protocols of the Department of Oral and Maxillofacial Surgery by the same surgeon for all procedures. At the end of the surgery, an anxiety scale was again recorded, and another memory card was shown. Additionally, a 100-mm quality-of-experience VAS was shown with “excellent sedation” on the left-hand edge and “poor sedation” on the right-hand edge. Participants were given a self-addressed stamped envelope with a questionnaire to be completed the day after surgery. Additionally, a form that showed pictures of viewed memory cards, as well as memory cards not viewed, was provided and participants were asked to circle those cards that they remember seeing during the surgical study session.

Postoperative pain medication, consisting of rofecoxib (Vioxx), 50 mg/d for 5 days as needed, was dispensed in addition to a written prescription for 6 tablets of a combination of hydrocodone, 5 mg, and acetaminophen, 500 mg, which was provided. Patients were discharged to a responsible escort following standard department discharge criteria.

Table 1. Mean $\pm$ SD Visual Analog Scale Anxiety Scores

	Triazolam	Zaleplon	<i>P</i> Value
Presedation	28.0 $\pm$ 20.8	34.1 $\pm$ 19.6	.95
Preoperative	22.3 $\pm$ 18.6	32.4 $\pm$ 22.1	.71
Postoperative	31.9 $\pm$ 29.2	46.4 $\pm$ 26.5	.35

Patients then returned to the Oral and Maxillofacial Surgery Clinic for the second surgical procedure at least 2 weeks after the initial surgical procedure. For the second surgery all protocols were identical except the other study drug was administered and different memory cards were shown. There was an additional item on the questionnaire to assess if there was any preference for sedative agent.

The VAS values were analyzed using an analysis of variance with drug and assessment period (with repeated measures) as the factors. Post hoc testing was performed using the Tukey-Kramer procedure. Memory card recall was assessed using the McNemar test. With a nondirectional α risk of .05 and a SD of 30 mm, a sample size of 14 subjects was necessary to demonstrate a difference in VAS score of ± 25 mm with a power of 80%.

RESULTS

Fourteen patients (5 females and 9 males) completed the study. Vital signs were stable for all patients. Mild tachycardia was noted after local anesthetic injections, which returned to baseline after a few minutes as expected. Oxygen saturation was never below 98% for any subject. All patients were conscious during the entire procedure and responded appropriately to verbal command. Surgery time was similar for both groups (18.1 $\pm$ 4.2 minutes for triazolam vs 16.7 $\pm$ 5.8 minutes for zaleplon; $P < .55$, dependent *t* test). Anxiety scores did not differ significantly at any of the time points (Table 1).

Quality of surgical experience by VAS, with lower scores indicating more comfort during surgery, was assessed on the postoperative questionnaire. For the first surgery, there was no statistically significant difference in quality of experience (33.2 $\pm$ 29.9 for triazolam vs 38.4 $\pm$ 32.5 for zaleplon; $P < .94$). For the second surgery, however, there was a trend toward a more

comfortable experience with triazolam (27.6 $\pm$ 20.8 for triazolam vs 49.6 $\pm$ 22.1 for zaleplon; $P < .0875$) (Table 2).

Amnesia was also evaluated by questionnaire via questions of recall of various events during surgery and by use of memory cards. All participants, except 1 triazolam-sedated patient, remembered the local anesthetic injections. All participants, except 2 triazolam-sedated patients, indicated that they recalled portions or all of their surgery. There was no statistically significant difference in recall of these events. A similar pattern was seen in memory card recall, where most patients could identify which memory cards they were shown (Table 3).

Postoperative effects were also studied. Only 1 patient in each group noted any unpleasant effects in recovery. Once home, there was a significant difference in lingering sedative effects. Eleven of the triazolam-sedated patients and 4 of the zaleplon-sedated patients felt the "sedative drugs lingered for the rest of the day" ($P < .016$). Nine of the zaleplon-sedated patients felt they were alert enough to return to normal activities "right when I got home," whereas only 3 of the triazolam-sedated patients felt the same way. All but 2 of the triazolam-sedated patients and the rest of the zaleplon-sedated patients felt they could return to normal activities by early evening. Two of the triazolam-sedated patients required a full night's sleep to feel alert enough to return to normal activity.

Of those who had a drug preference based on the final question on the second questionnaire, 8 participants (61.5%) preferred triazolam and 5 participants (38.5%) preferred zaleplon ($P < .58$ via exact binomial test). One participant felt both drugs provided good sedation and had no drug preference.

DISCUSSION

This study compared several characteristics of 2 oral sedatives and their clinical usefulness in a third molar extraction model. The methods of this study evaluated patient anxiety, comfort, memory loss, and surgical difficulty of the extractions and also accounted for age and weight of the patient by using a repeated-measures design. These studied parameters were then used to eval-

Table 2. Mean $\pm$ SD Visual Analog Scale Quality of Experience Scores*

	Triazolam	Zaleplon	<i>P</i> Value
First surgery	33.2 $\pm$ 29.9	38.4 $\pm$ 32.5	$< .94$
Second surgery	27.6 $\pm$ 20.8	49.6 $\pm$ 22.1	$< .0875$

* Zero indicates excellent experience.

Table 3. Number of Memory Cards Remembered Correctly

	Triazolam	Zaleplon	P Value
Presedation	13	14	>.99
Preoperative	11	13	>.99
Postoperative	11	13	>.99

uate this clinical effectiveness of each drug as an oral sedative. Triazolam has a long history of use as an oral sedative in dentistry, and many believe it to be close to an ideal oral agent due to its good sedative effects and favorable pharmacokinetic profile. It is well studied as a single-dose agent for sedation in dental procedures. Our hypothesis was that zaleplon would be equally effective but may have a more favorable recovery profile.

The only significant finding was, indeed, faster recovery with zaleplon versus triazolam as expected based on pharmacokinetic and pharmacodynamic information. Most of the triazolam-sedated patients (79%) did not feel recovered enough to return to normal function on arrival home, whereas most (64%) of the zaleplon-sedated patients felt they had fully recovered on home arrival. Although quick recovery is desirable, it is likely important to caution patients taking zaleplon that they may not be completely recovered for more complex psychomotor functions (eg, driving) even though they may feel fully recovered. Interestingly, 2 of the patients who took triazolam required a full night's sleep to return to normal function. This is concerning in light of recent recommendations by some groups to use much higher and multiple doses of triazolam for dental office sedation.

Both agents were similar in regard to relief of anxiety when using a self-reported VAS. This is important since the nonbenzodiazepine GABA_A agonists, such as zaleplon and zolpidem (Ambien), may have differential effects on central nervous system GABA receptors such that anxiolysis may not be as profound. Our preliminary findings seem to indicate that zaleplon anxiolysis is comparable to that achieved with triazolam. Since this is the primary function of oral sedation in dentistry (ie, anxiolysis vs true sedation), zaleplon appears effective for this purpose, at least compared with triazolam.

Quality of surgical experience showed a trend toward increased satisfaction in the triazolam-treated patients for the second surgery (27.6 ± 20.8 for triazolam vs 49.6 ± 22.1 for zaleplon; $P < .0875$; smaller value

more comfortable). Most likely, some of the triazolam-treated patients felt different, presumably due to less intraoperative sedation with zaleplon. Amnesia seems not to be the difference, since this was similar and uniformly poor with either drug as measured by memory cards. Additionally, when the overall experience was taken into account, no statistical difference of drug preference occurred. One interpretation is that the overall experience of *both* intraoperative sedation and recovery quality influenced the composite rating of the participants.

CONCLUSION

Zaleplon, 10 mg, provides comparable anxiolysis and overall quality of sedation to triazolam, 0.5 mg, in a third molar extraction surgical model. Amnesia is unlikely with either agent at these dosages. Recovery from zaleplon is, however, more rapid than that of triazolam.

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