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Expanded Studies of the Pharmacokinetics and Clinical Effects of Multi-dose Sublingual Triazolam in Healthy Volunteers

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Abstract

Previous work described the pharmacokinetics and clinical effects of multi-dose sublingual (SL) triazolam (Halcion®). This laboratory study evaluated the hypothesis that incremental dosing of triazolam produces dose-dependent central nervous system (CNS) depression that is profound and long lasting. Forty-nine healthy adults 21–39 years, not receiving dental treatment, were randomly assigned to placebo (n=12), or 1-of-3 triazolam groups (0.25 mg single dose, n=12; 0.5 mg divided between 2 equal doses over 60 minutes, n=12; or 0.75 mg divided among 3 doses over 90 minutes, n=13). Plasma triazolam concentrations were determined. Bispectral index (BIS) and the Observer Assessment of Alertness/Sedation (OAA/S) were used to assess sedation. Plasma triazolam concentrations increased with time in all subjects, with $T_{\max}$ and $C_{\max}$ both increasing dose-dependently. Compared to placebo, all dosing paradigms produced dose-dependent BIS suppression and sedation. The single dose of 0.25 mg reached its peak BIS suppression at 90 minutes (81 ± 7) and sedation at 120 minutes (3.6 ± 0.5), and returned to baseline before 360 minutes. In contrast, incremental dosing of 0.5 and 0.75 mg produced profound and long-lasting BIS suppression and sedation that did not plateau until either 180 or 210 minutes measured by BIS (67 ± 14 and 60 ± 16 at 0.5 and 0.75 mg, respectively) and 150 minutes measured by OAA/S (3.2 ± 1.0 and 2.7 ± 0.4 at 0.5 and 0.75 mg, respectively). These data more fully characterize the effects of incremental dosing with SL triazolam and provide additional insight for discharge safety recommendations.

Keywords

triazolam; sublingual; sedation; BIS; bispectral index; observer assessment of alertness/sedation (OAA/S)

INTRODUCTION

The incremental sublingual (SL) dosing of the benzodiazepine triazolam has become an increasingly popular approach dentists are using to sedate fearful patients. While originally

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indicated for treating insomnia, triazolam has a number of pharmacological, behavioral, and safety characteristics that make it well suited for use in dental settings.^{1–11} Compared to other benzodiazepines administered as a *single* dose, triazolam has a rapid onset, short duration of action, the ability to induce a somnolent state with minimal cardiovascular and respiratory depression, and reduces the ability of many patients to remember dental experiences that some consider aversive. Additionally, the commercial availability of the receptor antagonist flumazenil makes it possible to quickly reverse unwanted side effects produced by triazolam and other benzodiazepines.

While incremental dosing strategies for triazolam are increasingly being taught in continuing dental education courses, there are practically no data available to evaluate their safety or efficacy. We have reported on the safety and behavioral effects of a fixed-schedule, multi-dose regimen of triazolam (1.0 mg total dose) in healthy adults in a laboratory setting pilot study.¹² Those data suggest that if incremental sublingual (SL) dosing of triazolam is to be used in clinical practice, the monitored recovery period needs to be long enough to reasonably ensure that at a minimum the $T_{\max}$ (the time point at which peak plasma concentrations are achieved) has occurred and that the patient is sufficiently recovered, as indicated by diminishing levels of sedation to a point where their CNS depression is not a threat to their well-being when unsupervised. When determining when it is safe to discharge a patient after sedation, it is important to remember that there is a time lag between reaching the peak plasma concentration of triazolam and observing its maximum pharmacodynamic effect. A computer simulation of this property, known as “effect site equilibrium delay”, has been modeled for this incremental dosing condition of 1.0 mg of triazolam administered over 90 minutes.¹³ It predicts that the maximum pharmacodynamic effect would occur 3 hours after the initial dose, and is consistent with our experimental observations. In our previous investigation, incremental SL dosing of triazolam appeared to slow the rate of drug absorption but the study design did not allow determination of the $T_{\max}$ as subjects were only observed for 180 minutes.

Collectively, all of the factors described above led to this more comprehensive laboratory study, with the goal being to collect additional data that characterizes the sedation produced by incremental dosing of triazolam. As such, this double blind, placebo-controlled laboratory study was conducted to determine the time- and dose-dependent pharmacologic and behavioral characteristics of incrementally administered SL triazolam in healthy adults not receiving dental treatment.

MATERIALS AND METHODS

Subjects

Forty-nine healthy adults between the ages of 21 and 39 years participated. Study participants were selected consecutively from the pool of respondents answering a posted advertisement on campus for research subjects for a study about a sedative medication used in dentistry. Exclusion criteria included a medical history significant for systemic disease (American Society of Anesthesiologists Class II or greater), use of benzodiazepines, anxiolytics or any other medications that would interact with triazolam's metabolism or clinical effect (including herbals) within four weeks of the study, body mass index (BMI) less than 15 kg/m² or greater than 35 kg/m², pregnancy or not currently using pharmacologic methods of birth control, allergy or sensitivity to benzodiazepines, and chronic tobacco use. Those meeting the criteria and interested in participating in the study provided a self-reported medical history at a screening appointment prior to the day of the study. The Institutional Review Board of the University of Washington approved this study, and the informed consent of all participants was obtained. All participants were provided with a financial incentive for their participation.

Study Design and Procedures

Participants had no food or drink for at least 6 hours before beginning the study protocol. They were seated in a dental treatment room, had noninvasive monitors applied for measuring vital signs (blood pressure, heart rate, hemoglobin saturation), and their baseline vital signs were recorded. An intravenous (IV) catheter was then placed in either an arm or hand vein for blood sampling, and a baseline sample was obtained. No dental treatment was provided during this study. Participants were continuously monitored by a dentist anesthesiologist (KH).

Participants in this study were randomly assigned by a computerized algorithm to 1-of-4 SL dosing schemes: single SL triazolam dose of 0.25 mg, 2 incremental SL triazolam doses of 0.25 mg (total of 0.50 mg over 60 minutes), 3 incremental SL triazolam doses of 0.25 mg (total of 0.75 mg over 90 minutes) or inactive placebo (no triazolam). Table 1 defines the timing of dosing of triazolam and placebo for the 4 groups, with Group 1 serving as the “no drug” control. Group 2 was the “standard” control” in which a single SL tablet was given to reduce anxiety and produce sedation prior to the start of dental treatment. All subjects received a tablet at each time point. When not dosed with triazolam at 0, 60 and 90 minutes, a placebo compounded to be similar in form and color to the active drug was administered.

After the collection of all baseline data and samples, subjects received either 0.25 mg triazolam (Halcion®, Pharmacia & Upjohn Co., Kalamazoo, MI), or a placebo tablet with instructions to let the tablet dissolve under the tongue. Dissolution of the tablet was verified visually 2 to 3 minutes after dosing. Additional SL triazolam (0.25 mg) or placebo was administered with the same instructions 60 and 90 minutes later, as described in Table 1. The timing and amount of the 3 predetermined incremental triazolam doses were based on conversations with dentists who use incremental triazolam dosing strategies as part of their clinical practice. The study design included a second arm that evaluated the misinformation memory effect as a result of the various levels of benzodiazepine administered. The misinformation memory results have been presented elsewhere.¹⁴

Blood pressure, heart rate, respiratory rate, and hemoglobin saturation (SpO₂) were recorded at 30-minute intervals. Venous blood was also sampled at the same 30-minute intervals (11 samples per subject, approximately 3 mL each), and plasma prepared as previously described.¹²

Plasma triazolam concentrations were quantified by liquid chromatography-tandem mass spectrometry. In brief, 1 ng of d4-triazolam internal standard (Cerilliant, Round Rock, TX) and 0.75 mL 4% phosphoric acid were added to each 0.5 mL plasma sample, which was then applied to an Oasis MCX (Waters Corp, Milford, MA) 96 well extraction plate preconditioned with water and methanol. Plates were washed with 0.1M HCl then methanol, eluted with 2% ammonium hydroxide in methanol, eluants evaporated to dryness, and reconstituted in mobile phase (10 mM ammonium acetate: methanol, 70:30). Analysis was performed using a Shimadzu Prominence HPLC system (Kyoto, Japan) and Waters SunFire C18 2.1 × 50mm × 3.5μm analytical column and MetaGuard Polaris C8-A 2.0mm × 5μ guard column interfaced to an API/Sciex 3200 mass spectrometer (Applied Biosystems, Foster City, CA) with a Turbo Ion Source. The mobile phase gradient was 30 to 80% methanol over 4 min in 10 mM ammonium acetate (pH 4.25) at 0.25 mL/min and 30°C. The mass spectrometer was operated in turbo spray ionization mode using positive polarity. For triazolam and d4-triazolam, respectively, the transitions monitored were m/z 343→308 and 347→312, declustering potential was 76 and 71 V, entrance potential was 4.5 V for both, collision energy was 45 and 43 V, and exit potential was 26 and 30 V. Analytes eluted at 3.8 min. Triazolam was quantified using standard curves of peak area ratios, constructed using calibration standards 0.1 – 7.5 ng/mL. The interday coefficients of variation were 8, 5 and 4% at 0.25, 1 and 5 ng/mL, respectively.

Sedation was measured every 30 minutes after the first SL triazolam dose by a trained clinical observer (JP) using the Observer Assessment of Alertness/Sedation (OAA/S). The OAA/S determines the level of sedation using measures across four dimensions: responsiveness, speech, facial expression, and ocular appearance.¹⁷ The subject's composite score is derived from the lowest score in any of the four dimensions. The observer was blind to the subject's group assignment. A bispectral index monitor (BIS, Aspect Medical Systems, Newton, MA) was also applied to the forehead of each participant at baseline and used to assess triazolam-induced changes in the electroencephalogram (EEG). The BIS uses the frequency and amplitude of EEG signals to calculate a dimensionless index that ranges between 0 and 100, where 100 is fully awake and lower scores indicate diminished EEG activity.^{15–19} Our previous research has shown a strong relationship between OAA/S and BIS scores ($r=0.85$).¹² The study anesthesiologist recorded the BIS scores which were not shared with the clinical observer who performed the OAA/S.

Participants were not discharged for home until discharge criteria had been met, including no danger of compromising their airway, a sustained level of consciousness in which they engaged in purposeful verbal conversation, stable vital signs comparable to their baseline and able to stand and ambulate without assistance.

Data Analysis

All results are presented as the mean $\pm$ standard error (SE).

RESULTS

Subject and Procedure Descriptions

The mean age of the 49 subjects participating in this study was 25 years (range = 21–39 years). Their mean height and weight were 174 cm (range = 160–185 cm) and 73 kg (range = 56–95 kg), respectively. Mean BMI was 23 kg/m² (range = 19–31 kg/m²). Twenty of the 49 participants were female.

Plasma triazolam concentrations

Figure 1 displays the mean plasma triazolam concentrations as a function of the time after the first dose. With the exception of the no drug placebo control group, triazolam concentrations gradually increased in all subjects as a function of the dose and the time it was administered. No triazolam was detected in the plasma of the placebo group. For those in Group 2 (0.25 mg triazolam) $T_{\max}$ was 60 min and $C_{\max}$ was 2.1 ± 0.8 ng/mL (range at 60 minutes = 0.77–3.26 ng/mL). $T_{\max}$ was 150 min (90 minutes after the last dose) and $C_{\max}$ was 4.0 ± 1.6 ng/mL (range at 150 minutes: 2.3–7.2 ng/mL) in Group 3 (0.25 mg triazolam at 0 and 60 minutes). The $C_{\max}$ in Group 4 (0.25 mg triazolam at 0, 60 and 90 minutes) was 5.1 ± 1.6 ng/mL (range = 2.5–8.4 ng/mL). However, mean plasma triazolam concentrations were still increasing at 240 minutes in this group, suggesting that $T_{\max}$ most likely occurred between the 240 and 300-minute sampling periods (the time interval between plasma sampling was increased from 30 to 60 minutes, 240 minutes after the first dose). Plasma triazolam concentrations remained elevated at the end of the 6 hour observation period, averaging 0.9 ± 0.3 ng/mL (range 0.4–1.4), 2.9 ± 1.5 ng/mL (range 0.8–6.5) and 4.1 ± 1.6 ng/mL (range 1.6–7.4) in the 0.25, 0.5 and 0.75 mg dose groups, respectively. Interindividual variability in plasma concentration increased with triazolam dose.

Triazolam Clinical Effects

Dose-dependent CNS depression was observed in response to incremental SL dosing (Figure 2). Subjects in Group 2 receiving a single dose of triazolam (0.25 mg) had their lowest BIS

scores at 90 min (80) and maximal sedation at 120 minutes as measured by the OAA/S (3.6). Level of consciousness in this group returned to baseline by the end of data collection at 360 min. In Group 3, incremental SL dosing of 0.5 mg triazolam (0.25 mg at 0 and 60 min) produced the lowest BIS scores at 210 min (67) and maximal sedation at 150 min measured by OAA/S (3.2). The lowest BIS scores occurred at 180 or 210 min (60) and maximal sedation at 150 min as measured by OAA/S (2.7) in Group 4. Note a BIS score of 60 is regarded as the threshold for general anesthesia.

At no time during the study did any of the subjects experience changes in any of their vital signs greater than 15% of their baseline values (data not presented). Of greatest importance is that all measures of ventilation and tissue oxygenation were within normal and safe limits (no respiratory rates less than 12 breaths/minute, and no hemoglobin saturation values less than 96% breathing room air).

Discussion

An increase in the utilization of sedation medications by non-anesthesiologists, including dentists, has grown dramatically. This has been prompted, in part, by the need for pharmacological tools to address high levels of fear and anxiety about dental care among the US population. Unfortunately, the science base for the use of sedative drugs in dentistry has not kept pace with the applications in clinical practice resulting in increased risk to the public and concern among public policy makers. Therefore, new efficacious sedation approaches need to be developed and adequately studied that will effectively and safely enable the treatment needs of these fearful populations to be met within the confines of the current oral health workforce.

The results of this laboratory study are an extension of our previous work with healthy ASA I subjects¹² and computerized modeling.¹³ It provides new information about the early part of what would be the recovery period for dental patients sedated with an incremental dosing paradigm of SL triazolam. Even though no dental treatment was being performed in this laboratory study, it employs a more rigorous placebo controlled randomized design with three active drug dosing conditions and a larger sample size. This work will be the foundation of future clinical trials of this sedation technique in dental treatment settings with fearful patients.

Plasma triazolam concentrations following incremental SL dosing

The research literature suggests that the time to achieve peak plasma concentrations ($T_{\max}$) from a single SL or oral dose of 0.25 mg triazolam is 75 minutes.^{4, 20} In the current study, a single SL dose (0.25mg) of triazolam (Group 2) reached peak concentrations at 60 minutes (time range: 30–180 minutes; concentration range: 1.4–4.4 ng/mL). Based on the reported pharmacokinetics of a single administration, our previously reported results, and computerized modeling¹³ the peak concentration time ($T_{\max}$) in Groups 3 and 4 would have been expected at approximately 120 and 150 minutes, respectively. However, the current results show that more time was needed after the last incremental dose to reach $T_{\max}$ in these 2 groups and that this slower rate of absorption may not be a linear function. The $T_{\max}$ of Groups 3 and 4 (receiving 1 or 2 additional 0.25 mg doses in the 90 minutes after the initial dose) occurred at 150 and 240 minutes, respectively (Figure 1). The $T_{\max}$ across individual participants in Group 3 ranged from 90 to 300 minutes (concentration range: 2.8–7.6 ng/mL). Similarly, the $T_{\max}$ across individual participants in Group 4 ranged from 150 to 360 minutes (concentration range: 3.1–9.0 ng/mL). This is significant, especially for those subjects in Group 4 because the time interval between plasma sampling was increased from 30 to 60 minutes, 240 minutes into the study. This makes it difficult to determine the true $T_{\max}$ for this group since the plasma triazolam concentrations may have still been increasing for some subjects (the $T_{\max}$ value for 6 participants in this group occurred at either 240, 300 or 360 minutes). Even though the total

doses are different in this study compared to our previous published research, the results are consistent with our previous findings and computerized models^{12–13}, suggesting that incremental SL dosing of triazolam results in a slower rate of absorption compared to a single SL dose.

From the results described above, it is evident that there was substantial interindividual variability in plasma triazolam concentrations. Even though our exclusion criteria narrowly tailored our population of participants, there are likely to be other factors responsible for the variability we observed. The literature suggests that age, sex and common systemic medications may impact the pharmacokinetics of triazolam and other benzodiazepines.^{20–24} While our exclusion criteria limited extremes in age, it spanned 18 years in this study population (21–39 years of age). Another factor that may have contributed to the variability was the sex of the participants. Twenty of the 49 participants were female. While we excluded those with systemic diseases (American Society of Anesthesiologists Class II and above), it is possible that some of these healthy subjects may have been taking non-prescription drugs and/or herbal supplements that influenced the pharmacokinetics of triazolam, but were not accounted for in our screening process. Stratifying our results based on age and sex would produce smaller sub-groups from which it is difficult to draw meaningful conclusions. Our narrowly tailored study population is not likely to be representative of what dentists making decisions about whether SL triazolam dosing strategies are appropriate for all of the patients they will encounter in clinical practice. At a minimum, dentists are likely to encounter variations in age, BMI, physical status, concomitant use of prescription and non-prescription drugs, and dental fear, and future clinical studies will be needed to guide them in their decision making.

Dose-dependent CNS depression and BIS changes with SL titration of triazolam

Clinically, the sedative effect of a single SL dose of 0.25 mg triazolam is best characterized as minimal sedation in adults.²⁵ A single SL dose of triazolam resulted in maximal OAA/S scores between 3 and 4 in the current laboratory research. In contrast, multi-dose regimens of this drug administered over short time intervals are more likely to produce moderate to deep sedation, as supported by our previous research in which no dental treatment was being delivered.¹² This previously reported research demonstrated that multi-dosing regimens with triazolam could produce a level of CNS depression consistent with general anesthesia. The current study adds to the previous work by demonstrating that the mean recovery time for the multi-dose regimens is at least 360 minutes as measured by the OAA/S scores.

It has been suggested that EEG activity can be reflective of the sedation and psychomotor impairment produced by triazolam. Time-dependent changes in the Digit-Symbol Substitution Test (DSST), a measure used to assess psychomotor impairment, have been shown to be strongly correlated with EEG changes and plasma concentrations of triazolam.²⁶ Instead of using EEG, our study used BIS to assess sedation-related changes in the EEG. BIS uses the frequency and amplitude of EEG signals to calculate a dimensionless index in which decreasing scores are associated with CNS depression. Seeing that the BIS scores in Groups 3 and 4 had not yet returned to their baseline levels at 360 minutes, it is probable that if EEG activity had also been measured, it would have been consistent with at least mild sedation and some psychomotor impairment. This emphasizes the need to carefully assess each patient before discharge to make sure their degree of psychomotor impairment is minimal and they are not in danger of hurting themselves with little or no supervision.

This laboratory study was not designed to simulate actual clinical practice where dental care is provided. The stimulation associated with intraoral injections and treatments with instruments like the dental handpiece (i.e., drill) will likely diminish the level of sedation produced by benzodiazepines, especially in those patients fearful of dental treatment. On the other hand, there are often extended periods during dental treatment when the mechanical and

auditory stimulation is much less or completely absent. It is likely during periods of minimal or no mechanical and auditory stimulation that patients receiving incremental dosing regimens might be over sedated. When mechanical and auditory stimulation resume, most patients will probably return to a lighter level of sedation. However, some patients may need more definitive support and rescue interventions. The initiation of basic life support (BLS) skills should always be the first intervention, and include opening and maintaining a patent airway and providing positive pressure ventilation if indicated. Pharmacologic intervention with the competitive benzodiazepine receptor antagonist flumazenil is indicated once it has been determined that these BLS measures are not sufficient. Because flumazenil is to be administered via the intravenous route, and establishing venous access is not a skill most general dentists have, research is needed to determine the most safe and effective pharmacologic rescue strategies that can be used by general dentists in these situations.²⁷

It is also important to note that this laboratory study differed from clinical practice in that the fixed dosing schedule of the protocol did not allow for clinical judgment about when to administer additional doses of triazolam or the amount at those times. In clinical practice, these decisions would have been based on the patient's response to their surroundings and/or reported anxiety, and the dentist's level of skill and experience.

One area of concern to practicing dentists that use incremental dosing techniques is the perceived need at times to administer total doses in excess of the maximum recommended dose (MRD). The MRD is the maximum FDA-recommended dose of a drug in FDA-approved labeling for unmonitored home use. Outpatient IV sedation in dental practice has a long record of safely employing larger doses of benzodiazepines than is common in hospital anesthesia practice because of the stimulation involved with treatment.⁴ This experience with the IV use of high doses of benzodiazepines in dental practice is supportive, in theory, of the need to administer SL doses of benzodiazepines in excess of the MRD in similarly stimulating clinical settings with comparable safety and efficacy.

Results of these pharmacokinetic and clinical data at 360 minutes suggest that patients should be monitored until this time point at a minimum when the total incrementally administered dose is given within a time period of 60 to 90 minutes. All of these data in which the total incremental dose of 0.5 and 0.75 mg of triazolam were administered within a 60 to 90 minute window of time are consistent with the clinical judgment of it being unsafe to discharge a patient earlier than 6 hours after the first dose. Similar admonishments have been made after our assessments of similar clinical approaches with children in the dental office.^{8, 28}

Conclusion

The current clinical application of incremental dosing with SL triazolam in dentistry has moved ahead of an adequate research foundation. The current laboratory study extends findings from our previous work in identifying the $T_{\max}$ and $C_{\max}$ for doses of triazolam currently being administered in the clinical setting.¹² Clinical studies are being planned that will fully characterize the pharmacokinetics and clinical effects of incremental dosing with triazolam in dental treatment settings with fearful patients. The goal of these future studies will be to develop evidence-based guidelines for selecting appropriate patients, triazolam doses, discharge criteria and related safety recommendations.

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Figure 1.

Plasma concentrations of triazolam following incremental sublingual administration. After a baseline blood sample was collected, plasma samples were then collected every 30 minutes for the first 4 hour time period and then each hour for the final 2 hours of the study.

Figure 2. CNS depression/sedation as measured by OAA/S (Panel A), and EEG amplitude and frequency changes as measured by BIS (Panel B). Dose dependent CNS effects were produced by triazolam following incremental sublingual administration.

Table 1

Treatment groups and triazolam dosing schedule.

Dosing Time (minutes)	Group 1 (placebo: control)	Group 2 (total dose: 0.25 mg)	Group 3 (total dose: 0.5 mg)	Group 4 (total dose: 0.75 mg)
0	placebo	0.25mg	0.25mg	0.25mg
60	placebo	placebo	0.25mg	0.25mg
90	placebo	placebo	placebo	0.25mg