

Hallucinations and Delirium in the Dental Office Following Triazolam Administration

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A rare and unusual case of hallucinations following triazolam administration is reported. A review of the literature suggests that hallucinations following triazolam are rare; this is the first report of such a reaction when triazolam was used for oral conscious sedation in dentistry. A discussion of dental implications follows with emphasis on complete medical history evaluation before administering oral sedatives. We conclude that the proper selection of oral sedation candidates, coupled with recognition and management of adverse events, is essential.

Key Words: Triazolam; Hallucinations; Oral sedation.

INTRODUCTION

Enteral (oral) conscious sedation has recently gained increased popularity as a treatment modality for adult dental patients. At the forefront of the technique is the drug triazolam which, despite a colorful history has emerged as a "near-ideal" agent for use as an in-office sedative.¹ As more dentists provide oral sedation, the number of adverse events will increase.

Triazolam is a short-acting benzodiazepine with a pharmacokinetic profile favorable for oral sedation. The time to maximum concentration in plasma and the elimination half-life of triazolam are 1.25 hours and 3 hours respectively.² Furthermore, because of the wide margin of safety inherent to the benzodiazepines, triazolam can safely be administered to dental patients with the expectation of anxiolysis and increased acceptance of dental procedures. With careful case review, practitioners can minimize the likelihood of potential morbidity. However, when patients fail to disclose accurate medical history information, the dentist can unfortunately be confronted with unexpected drug reactions.

A review of the literature illustrates several cases of hallucinations involving the accepted indication (insomnia) of triazolam. In 1979, van der Kroef⁴ described tri-

azolam as potentiating a "syndrome" that included reactions such as "depersonalisation, derealisation, depression, and hypnagogic hallucinations." Although van der Kroef was criticized for the lack of validity of his claims, his accounts marked the beginning of controversy involving triazolam and delirium.^{4,5}

Delirium involves a failure of cognitive function characterized by confusion, disordered speech, and hallucinations.⁷ Einarson⁸ described a case in which a 79-year-old female experienced visual and auditory hallucinations after administration of 0.25 mg triazolam for the treatment of insomnia. Several years later Einarson⁸ also documented a case in which hallucinations manifested shortly after triazolam administration. In this instance, a 56-year-old female was administered 0.5 mg triazolam concomitantly with cimetidine, a known cytochrome P450 3A4 inhibitor capable of slowing the metabolism and increasing the maximum plasma concentration of triazolam, and imipramine, a second generation tricyclic antidepressant. Auditory, visual, and tactile hallucinations developed and persisted for several hours. Neither patient experienced a depression of vital signs, and resolution was complete without recurrence of symptoms after benzodiazepine use was discontinued.

A further example of triazolam hallucinations was reported by Tokinaga and colleagues⁹ in which a patient received 0.25 mg triazolam to treat insomnia. On the 13th day of drug therapy, the patient's antibiotic regi-

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men was switched to erythromycin 600 mg/d, which precipitated visual hallucinations on the 14th and 15th days. Triazolam was discontinued on the 15th day and replaced with nitrazepam 5 mg. Hallucinations persisted for an additional two days until all benzodiazepines were discontinued and haloperidol 2 mg/d was administered. It was speculated by the authors that triazolam and nitrazepam metabolism was inhibited by erythromycin resulting in a greater effect than was anticipated.

Hallucinations have also been documented following withdrawal from triazolam. Heritech and colleagues¹⁰ described a case in which a 53-year-old male with a history of alcoholism exhibited psychosis and delirium. The patient had been taking excessive amounts of triazolam (up to 6 mg/d) for the treatment of insomnia, and once the drug was discontinued, bizarre behavior resulted. Fleming¹¹ also documented a case in which a patient was self-administering up to 5 mg/d of triazolam. Upon periods of drug abstinence, the patient reported tremors, changes in cognitive function, and cravings for the drug.^{9,10}

A strange reaction was described by Nevins¹² in which a patient experienced musical hallucinations after triazolam use. The 57-year-old man used 0.25 mg triazolam for 8 consecutive nights, after which the drug was discontinued. On the first night after discontinuing the medication, the patient experienced musical hallucinations consisting of the repetitive hearing of 15-20 familiar Italian songs. No visual, neurologic, behavioral, or memory disturbances were noted. The symptoms persisted for many months before dissipating.

Given the large number of prescriptions written, hallucinations involving triazolam may be considered rare or may simply be underreported. Further, they appear to be the result of the following factor(s): excessive dosing, drug-drug interaction, acute withdrawal, or idiosyncrasy. We present a case of hallucinations and delirium following the administration of triazolam for the purpose of oral conscious sedation in the dental office.

CASE REPORT

A 49-year-old Caucasian man presented to our private dental office with a complaint of acute pain from the left side of the mandible. Radiographic examination revealed a carious exposure of tooth #19 with an associated apical inflammatory lesion and buccal sinus tract. The options for treatment were explained to the patient and extraction was agreed upon. The patient requested oral conscious sedation for the procedure and a complete presedation work-up ensued. The medical history revealed a bilateral hip replacement, of which the patient was 6 days postdischarge from the hospital (16

days postsurgery), and a history of alcoholism and hypercholesterolemia. The patient had existing intravenous access in his left arm for the administration of antibiotics during the postoperative period of his hip procedure. The patient reported taking usual dosages of famotidine, simvastatin, OxyContin (oxycodone 20 mg controlled-release tablets), and Roxicodone (oxycodone 5 mg immediate-release tablets), as well as receiving intravenous infusions of levofloxacin and vancomycin. Upon further investigation it was learned that while the patient was in the hospital for treatment of his hip, he had a adverse reaction to morphine. While sleeping the patient became disoriented and confused, thinking he was at home. He proceeded to get out of bed and injured the hips that had just undergone repair. His pain medications were subsequently changed and the disorientation disappeared.

The patient was a long-time client of the practice, and had previously received oral sedation using triazolam at a total dose of 0.5 mg without incident. We consulted the patient's physician to determine the appropriate antibiotic prophylaxis needed after his joint replacement, and 2.0 g of amoxicillin was agreed upon. The patient also had a history of alcoholism (clean for 10 years), and extensive questioning into recent habits was completed with nothing significant noted. Baseline vital signs were recorded as follows: blood pressure 125/78 mmHg, pulse 90, and SaO₂ 99%. We felt the patient was an acceptable candidate for oral sedation, and specific preoperative instructions were given with emphasis on discontinuing OxyContin and Roxicodone the night before the procedure. To avoid the possibility of synergistic CNS depression, the patient was instructed to take ibuprofen 600 mg for analgesia the day of sedation dentistry. The sedation visit was scheduled for 2 days after the presedation interview and work-up.

The morning of the procedure the patient arrived at the office at 8 AM and was immediately administered 0.25 mg triazolam. After approximately 1 hour, the sedation level of the patient was assessed and deemed unacceptable (ie, anxiety was not sufficiently diminished to begin treatment), so another 0.25 mg tablet was administered. The patient began to display signs of slurred speech and disorientation 30 minutes after the second dose of triazolam, and treatment was attempted when patient responses and visual assessment indicated an acceptable sedation level. Quickly the disorientation of the patient progressed to confusion and frank visual and auditory hallucinations that could not be negated by physical or verbal stimulation.

It was our belief that the patient was having a severe reaction to triazolam, so we decided to administer flumazenil, the benzodiazepine reversal agent. An initial dose of 0.2 mg of flumazenil was administered via the

patient's semipermanent intravenous catheter and flushed with 2-3 mL of normal saline. This was followed by an identical 0.2 mg dose 5 minutes later, when no resolution or change in symptoms was observed. Hallucinations continued for the next 5 hours during which time the vital signs of the patient remained normal and airway patency was uncompromised. Because the patient's vital signs appeared stable, further flumazenil was not deemed necessary nor did we summon paramedics or contact the patient's physician during this time. Knowing the duration of action and half-life of triazolam, we monitored the patient both visually and using pulse oximetry until the drug was metabolized. We administered supportive care as needed until the hallucinations ceased. At no time did his behavior become violent, and there was no concern of injury either to him or to the dental staff. After the patient had seemingly regained normal cognitive function and the hallucinations had stopped, we released him to his family. The patient was delivered to the car by a wheelchair, and he was transported home without incident.

Because of the reaction witnessed and to ensure safe transportation, members of the dental staff accompanied the patient home. After the patient was safely home, we questioned his mother regarding the use of pain medication. Multiple pill bottles were inspected, the most recent being an empty container for 60 tablets of Roxicodone filled 2 days before the sedation appointment. His mother stated that the patient was taking pills "by the handful," and it was suspected that he had consumed the entirety of the prescription over the previous 48 hours. This was in considerable excess of the prescribed dose of 2 or 3 tablets every 4-6 hours as needed for pain. We notified both the pharmacy where the prescription was filled, and the prescribing physician of the drug overuse. A trained member of our staff monitored the patient until the patient's nurse practitioner arrived to administer his intravenous antibiotics. She was informed of the suspected overuse of prescription pain medications, and agreed to monitor the patient for recurrence of symptoms and to notify our office or emergency medical services should the need arise.

When we contacted the patient the next day, he confessed to lying on his health history and to self-administering excessive quantities of narcotic pain medication. He reported no memory of the previous day's events.

DISCUSSION

It is likely that this case involved a drug interaction between triazolam and oxycodone, rather than oxycodone overuse alone. Although the literature is replete with case reports of narcotic overuses precipitating halluci-

natory behavior, the patient's use of triazolam and oxycodone was viewed by the constraint of temporal logic which states that effects cannot precede their causes. The patient displayed no evidence of hallucinations during either the initial appointment or the preoperative period. Hallucinations began only after the administration of triazolam; and they disappeared once enough time had elapsed for the drug to be cleared. The patient's vital signs were never compromised at any time during the appointment. Cognitive failure manifested as hallucinations, paranoia, agitation, and amnesia. These features are consistent with, but less severe than, the "triazolam syndrome" described by van der Kroef and Einarson.^{3,8}

Triazolam has also been implicated in disinhibitory behavior and "dyscontrol." Disinhibition can be defined as "losing the ability to impose restraint upon oneself or one's activities, which then interferes with one's ability to function or constitutes a hazard to oneself or to others."⁴ It is postulated that benzodiazepines such as triazolam specifically, can induce a disinhibitory state similar to alcohol intoxication.¹³ The patient did not display disinhibitory behavior; rather, his responses and behavior seemed to be the result of his subjective perception of events not actually taking place.

This case report has several dental implications. Stated previously, as more oral sedation procedures are performed the number of adverse events will increase. As such, appropriate management of adverse events will become an even more critical part of sedation training and licensure requirements. Furthermore, management of adverse events can sometimes be mitigated with the use of emergency drugs. In the case of triazolam, the pharmacologic antagonist flumazenil should be readily available. The flumazenil package insert¹³ stipulates a 0.2 mg intravenous dose followed by subsequent doses 45 seconds later if the desired level of consciousness is not achieved. Since our patient was experiencing no respiratory distress and vital signs were normal, the intent of flumazenil administration was to break the hallucinatory activity. After 0.4 mg of flumazenil was administered without discernable change in the patient's behavior, we decided not to deliver additional flumazenil.

If we had observed depression of vital signs, or the patient had lapsed into unconsciousness, the standard algorithm for overdose (unknown drug other than benzodiazepines) would have involved the maintenance of a patent airway and positive pressure ventilation with 100% oxygen if necessary, maintenance of circulation, immediate activation of emergency services, and the administration of the narcotic antagonist naloxone. However, if the narcotic antagonist naloxone were administered, the outcome may have been different. If the patient was indeed abusing narcotic pain medications to

the level we suspected, a dose of naloxone may have precipitated acute withdrawal symptoms, which may have included hypertension, tachycardia, tremors, and convulsions, but could have been life-saving in view of a narcotic overdose.

The challenge for the dentist who performs oral sedation, or any treatment on a patient, is to gather data and complete a thorough past medical history. When an accurate medical history is not received, the safety of the sedative procedure can be compromised, and the patient can be exposed to unnecessary risk. Ultimately the responsibility falls upon the practitioner to collect medical history data, but occasionally the patient either neglects to divulge information or lies about the lack of pertinent findings. An incomplete medical history can often have a direct impact on treatment. In a survey by McDaniel and others,¹⁵ the most common negative response on a dental health history form involved admission of drug abuse. Furthermore, 10% of respondents felt dental health professionals did not need to be fully aware of a patient's health status. In our case, the patient neglected to inform us of his drug abuse even after the possible effects of narcotics and triazolam were discussed. Regardless, the case described above is an example of a failure on the part of the dentist to obtain and verify medical history information. When complete medical history information from the patient is in question, the practitioner should postpone all treatment until such information is made clear.

CONCLUSIONS

The administration of an oral sedative can be an effective means to alleviate or diminish anxiety and fear in dental patients. When patients are selected properly and dental personnel are trained to recognize and manage medical emergencies, the safety of oral sedation is increased and unexpected events can be minimized. We believe the drug interaction between triazolam and narcotic pain medications precipitated hallucinations and delirium in our patient. This case illustrates the need for complete medical history information as a first-line de-

fense in preventing untoward events associated with oral sedation for dentistry.

REFERENCES

1. Dionne RA, Trapp LD. Oral and rectal sedation. In: Dionne RA, Phero JC, Becker DE, eds. *Management of Pain and Anxiety in the Dental Office*. Philadelphia, PA: WB Saunders; 2002:225-234.
2. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet*. 1989;16:337-364.
3. Van der Kroef C. Reactions to triazolam. *Lancet*. 1979;2:526.
4. Rothschild AJ. Disinhibition, amnesic reactions, and other adverse reactions secondary to triazolam: a review of the literature. *J Clin Psychiatry*. 1992;12(suppl):69-79.
5. Lasagna L. The Halcion story: trial by media. *Lancet*. 1980;1:815-816.
6. Bruera E, Schoeller T, Montejo G. Organic hallucinosis in patients receiving high doses of opiates for cancer pain. *Pain*. 1992;48:397-399.
7. Einarson TR. Hallucinations from triazolam. *Drug Intel Clin Pharm*. 1980;14:714-715.
8. Einarson TR, Yoder ES. Triazolam psychosis—a syndrome? *Drug Intel Clin Pharm*. 1982;16:330.
9. Tokinaga N, Tsuyoshi K, Kaneko S, Otani K, Mihara K, Morita S. Hallucinations after a therapeutic dose of benzodiazepine hypnotics with co-administration of erythromycin. *Psychiatry Clin Neurosci*. 1996;50:337-339.
10. Heritech AJ, Capwell R, Roy-Byrne PP. A case of psychosis and delirium following withdrawal from triazolam. *J Clin Psychiatry*. 1987;48:168-169.
11. Fleming JAE. Triazolam abuse. *Can Med Assoc J*. 1983;129:324-325.
12. Nevins MA. Musical hallucinations and triazolam use. *NJ Med*. 1991;88:907-908.
13. Fillmore MT, Rush CR, Kelly TH, Hays L. Triazolam impairs inhibitory control of behavior in humans. *Exp Clin Psychopharm*. 2001;9:363-371.
14. Romazicon [package insert]. Nutley, NJ: Roche Laboratories; 1993.
15. McDaniel TF, Miller D, Jones R, Davis, M. Assessing patient willingness to reveal health history information. *J Am Dent Assoc*. 1995;126:375-379.