Side effects of triazolam in children

Susan E. Coldwell, PhD Kyoko Awamura, DDS, MPH, MSD Peter Milgrom, DDS Kristine S. Depner, BS Eliezer Kaufman, DDS Karen L. Preston, OD Helen W. Karl, MD

Dr. Coldwell is an assistant professor, Department of Dental Public Health Sciences, Dr. Awamura is clinical instructor, Department of Pediatric Dentistry, Dr. Milgrom is professor, Department of Dental Public Health Sciences, Ms. Depner is a student, Department of Pediatric Dentistry, University of Washington, Seattle, Washington, Dr. Kaufman is professor, Department of Oral Medicine, Hadassah-Hebrew University School of Dentistry, Jerusalem, Israel, Dr. Preston is a pediatric optometrist at The Children's Eye Doctors Redmond, Washington, and Dr. Karl is assistant professor, Department of Anesthesiology, Children's Hospital and Medical Center, Seattle, Washington.

Abstract

Purpose: *This study examined the incidence of side effects occurring with three doses of orally administered triazolam in children undergoing restorative dental procedures.*

Methods: *Thirty children, aged 39–81 months, participated in the study. The children were pretested for gait ataxia, amnesia, visual acuity, stereoscopic depth perception, and diplopia during a screening session. In a subsequent appointment, children received one of three triazolam dosages (0.005, 0.015, and 0.030 mg/kg) prior to dental treatment. Dosage assignment was random and double blind. Each child received a single triazolam dosage. Tests for gait ataxia, amnesia, and visual disturbances were repeated following drug administration.*

Results: *The proportion of children experiencing ataxia, amnesia, and diplopia increased with increasing triazolam dosages. The 0.030-mg/kg triazolam dosage impaired visual acuity and stereoscopic depth perception.*

Conclusion: *Triazolam produces ataxia, amnesia, and diplopia in a dose-dependent manner in children. (Pediatr Dent, 21:18–25, 1999)*

Recently, there has been much interest in the use of short-acting benzodiazepines to control anxiety in children undergoing minor surgical procedures. Dentists, in particular, have endorsed the use of midazolam and triazolam with fearful pediatric patients.[1–6] While the benzodiazepines carry a lower risk of respiratory depression than other sedative agents, a number of other side effects have been reported. These side effects include ataxia and anterograde amnesia, as well as daytime anxiety and rebound insomnia upon termination of drug use.[7, 8] "Disinhibitory effects" including extreme upset, anger, and aggressive behavior have also been reported, particularly in younger patients.[9] In addition, high doses of benzodiazepines are known to produce blurred vision and diplopia.[8, 10–13]

A number of pharmacological agents, including the benzodiazepines, produce diplopia when used at sedative dosages.[11, 12] Diplopia results from a loss of extraocular motor balance following decreased muscle tone in the medial recti, which normally prevent the eyes from diverging.[12] Harrington-Kiff[12] suggested that recovery from anesthesia following dental out-patient surgery may be readily monitored by testing for recovery of extraocular motor balance. The typical method for measuring oculomotor balance in pharmacological studies has been the Maddox wing test.[12, 13] However, this test requires some sophistication on the part of the subject, and is difficult to administer in children 6 years and younger.[12] The Worth 4-Dot test and Titmus stereoacuity tests are commonly used to assess diplopia and binocular fusion in ophthalmology studies with young children.[14–17] If these tests are to be used to measure pharmacological effects, pretesting must be done since there is evidence that some children have difficulty with these tests.[18–20]

Despite their potential usefulness, visual testing is not the typical method for monitoring recovery of pediatric dental patients. Behavioral measures that are more commonly used to determine that a child is ready for discharge following sedation include the ability to walk with limited aid, the ability to sit upright unaided, and the ability to speak normally.[21] These assessments do not require sophisticated testing, but rather may be accomplished by monitoring the normal behavior of the child.

Several studies have examined the safety of oral triazolam in children. Quarnstrom, Milgrom, and Moore[22] report that children given 0.005–0.022 mg/kg triazolam experienced no airway obstructions or reduction in oxygen saturation lower than 90%. Likewise, Meyer, Mourino, and Farrington[3] reported no significant side effects or significant reduction in oxygen saturation in children given 0.020 mg/kg triazolam

with 50% nitrous oxide. Karl and colleagues[23] report that children administered 0.025 mg/kg triazolam for dental procedures maintained oxygen saturation at 97–99% and were responsive to verbal instructions during a dental procedure.

While an optimum dose of triazolam has not been established for use in pediatric dentistry, some dosing guidelines have been suggested in the literature. Berthold and colleagues[24] recommended 0.005 - 0.006 mg/kg triazolam and 30–40% nitrous oxide for reduction of dental anxiety in children. This recommendation was based on an extrapolation of the adult dosage used in a study of mildly anxious adults undergoing oral surgery. In an uncontrolled clinical study, Quarnstrom and colleagues[22] reported that a group of children who were given an average dose of 0.014 mg/kg triazolam were more manageable for dental procedures than a group of children who were given an average dose of 0.010 mg/kg. Meyer and colleagues[3] report that 0.02 mg/kg triazolam with 50% nitrous oxide is as effective as 40 mg/kg chloral hydrate with 25 mg hydroxyzine and 50% nitrous oxide. However, they also state that the 0.02-mg/kg dose is near the minimal recommended levels, and suggest that a higher triazolam dosage may be warranted.

While the safety of triazolam has been established and some dosing data are available, other effects of triazolam, such as gait ataxia, anterograde amnesia, and visual disturbances have been under studied in young children. These side effects of triazolam delay discharge of children following sedation. They may also be upsetting to children and therefore have the potential to detract from the anxiolytic properties of the medication. Few sedation studies using benzodiazepines in pediatric dentistry have greater than a 70% success rate.[3, 22, 25, 26] When the success of sedation is not adequate, it is tempting for clinicians to increase the dose of the medication, hoping for more cooperative behavior. A consequence of using higher dosages may be a higher incidence of side effects. In this study, we determined the incidence of gait ataxia, anterograde amnesia, and visual disturbances occurring with three doses of orally administered triazolam (Halcion®, Upjohn, Kalamazoo, MI) in children undergoing restorative dental procedures.

Methods

Subjects

The subjects were 30 children (15 male and 15 female) between the ages of 39–81 months (mean age 60 months). The children weighed between 14.4 and 36.6 kg (mean weight 19.3 kg). Each child was in need of restorative dental treatment, had no contraindications for the use of triazolam (e.g., glaucoma), and was not currently taking erythromycin. Children were referred to the study either because of a history of uncooperative behavior in the Pediatric Dentistry Clinic or through public service announcements in the community offering care for fearful children. The Human Subjects Review Committee at the University of Washington approved this study. The procedures, possible discomforts or risks, as well as possible benefits, were fully explained to the children and guardians involved, and informed written consent was obtained from the guardians of each child prior to the investigation. The drug trial was carried out under IND #0357897 from the US Food and Drug Administration (FDA).

Procedure

Triazolam administration

Triazolam was held in a grape Kool-Aid®/sorbitol suspension. Suspensions were prepared by the University of Washington Medical Center Investigational Drug Services (IDS). Staff at the IDS prepared a concentrated suspension by combining finely crushed triazolam tablets (0.5 mg triazolam per mL of concentrate solution) with sugar free grape Kool-Aid powder (0.1 g Kool-Aid per mL of solution) and 70% sorbitol solution. Fresh concentrated suspension was made each week. This concentrate was subsequently diluted by IDS to produce the appropriate individual mg/kg dose for each child. Remaining concentrate was frozen at the end of each week and held for subsequent analysis for triazolam using gas chromatography.[23] The suspension was administered orally by the pediatric dentist, who squirted it into each child's mouth from a syringe. The syringe was subsequently refilled with plain Kool-Aid, which was also orally administered to the child to ensure that the entire triazolam dose was administered. In order to enhance compliance, children practiced this procedure with plain Kool-Aid during the preparatory visit. Following triazolam administration, the children watched a video tape of their choice for 30 min while sitting in the dental chair.

Throughout the procedure, the children were monitored following the American Academy of Pediatric Dentistry guidelines for the elective use of pharmacologic conscious sedation and deep sedation in pediatric dental patients, May 1996.[27]

Side-effects measures

Ataxia. Gait ataxia was assessed by having the children walk along a 6-ft. straight red line, which was taped to the floor. Scuffing, stamping, tripping, and inability to regain balance while walking were considered signs of gait ataxia.[28] Gait ataxia was scored as present or absent.

Amnesia. Anterograde amnesia was measured following a modification of the protocol developed by Flaitz, Nowak, and Hicks.[29] The measure was modified to increase its reliability by pretesting the children prior

to the drug trial. Before the dental procedure, each child was shown a colorful toy for 30 s. The children were encouraged to touch the object and comments about the toy were directed to them. Following a 60-min delay (during which dental treatment occurred), each child was asked to select that item from a series of five distinctive toys arranged randomly in another room. This procedure was repeated on the day of triazolam administration with five different toys than were used during the memory pretest. The toys used in pretest were a rubber clown (memory stimulus), a stuffed cat, a beach ball, a dump truck, and a plastic guitar (distracters). The toys used following drug administration were a stuffed monkey (memory stimulus), a dinosaur, a football, a fire truck, and a plastic xylophone (distracters). Anterograde amnesia was scored as present or absent.

Visual testing battery

Visual acuity. Binocular visual acuity was tested using the near-point Allen Picture Card at a distance of 33.8 cm.[30] The Allen card consisted of a graded acuity chart with several commonly identifiable line drawings ranging from 20/200 to 20/30 in Snellen equivalents. Each child was shown an 11.5- x 12.5-cm black-and-white demonstration drawing of a bird that matched one of the test figures. The child was asked to verbally identify the demonstration picture and subsequently search for and point to the bird in each of the rows on the graded test card. Each row contained successively smaller images. The last line in which a child could successfully point to the correct image was taken to indicate his/her level of visual acuity. Visual acuity was scored as 0, 1, 2, 3, 4, 5, or 6. These scores correspond to Snellen visual acuity's of 20/200, 20/160, 20/100, 20/80, 20/60, 20/40, and 20/30, respectively.

Stereoscopic depth perception. Stereoscopic depth perception was tested because a decrease in stereo vision is suggestive of a loss of binocular fusion. Stereo testing was accomplished using the circles portion of the Stereo Fly 3-D Vectogram® (Stereo Optical Co., Inc., Chicago, IL).[31] Children observed the test stimuli through polarized lenses from a distance of 42 cm. The polarized lenses allowed slightly disparate stimuli to be shown to the two eyes, giving rise to perceived depth. If binocular fusion was impaired, the images appeared flat. Children were shown a graded series of nine sets of four circles, and asked to point to the circle closest to them (the one with perceived depth). Children were assigned a score from 0 to 9 according to the number of dots they correctly identified before a mistake was made. These scores correspond to an inability to perceive stereoscopic depth (0) or the ability to perceive angles of stereopsis of 800, 400, 200, 140, 100, 80, 60, 50, and 40 s respectively.

Worth Four-Dot. The Worth Four-Dot is a test of binocular fusion that can indicate normal fusion, diplopia, or monocular suppression.[32]The test target was a filtered flashlight that revealed four 6-mm diameter dots around a 32-mm diameter circle. There were two green dots, one red dot, and one white dot. Each child wore a pair of glasses that placed a red filter over the right eye and a green filter over the left eye. The red filter allowed the right eye to see only two red dots (the red and white dot both appear red, the green dots are invisible) and the green filter allowed the left eye to see three green dots (the two green dots and the white dot appear green, while the one red dot disappears). If the children could fuse the information from both eyes properly, they saw four dots (one red, two green, and one that appeared to be a mixture of the two). Children with double vision saw five dots (two red and three green), while children with suppression of the right eye saw only two red dots and children with left eye suppression saw only three green dots. Each child was instructed to count the number of dots and to identify the color of each dot. If a child was unable to count, he/she was asked to point to each dot. Testing was performed in dim light at two distances, 41.6 cm and 1 m. At each distance, children were tested first with both eyes open, then with each eye covered in turn to test the accuracy of responses.

Protocol

At least one day prior to their restorative dental procedure, each child was evaluated at the University of Washington Pediatric Dentistry Clinic. The evaluation included visual examination, radiographic evaluation when indicated, rubber cup prophylaxis, and fluoride treatment. At this time, the children were weighed and each child was pretested on the side effects measures by a research fellow who had been trained to perform the vision tests by a pediatric optometrist.

Restorative treatment and postsedation side-effects testing took place in the University of Washington Dental Fears Research Clinic. Fig 1. presents a timeline of events occurring on the day of restorative treatment. IDS randomly assigned children to one of three

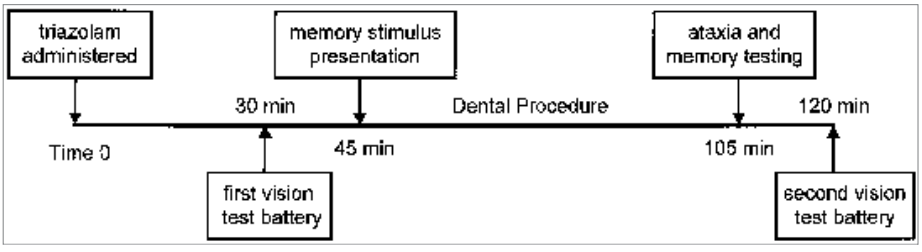

Fig 1. A time-line of events occurring on the day of restorative dental treatment is shown.

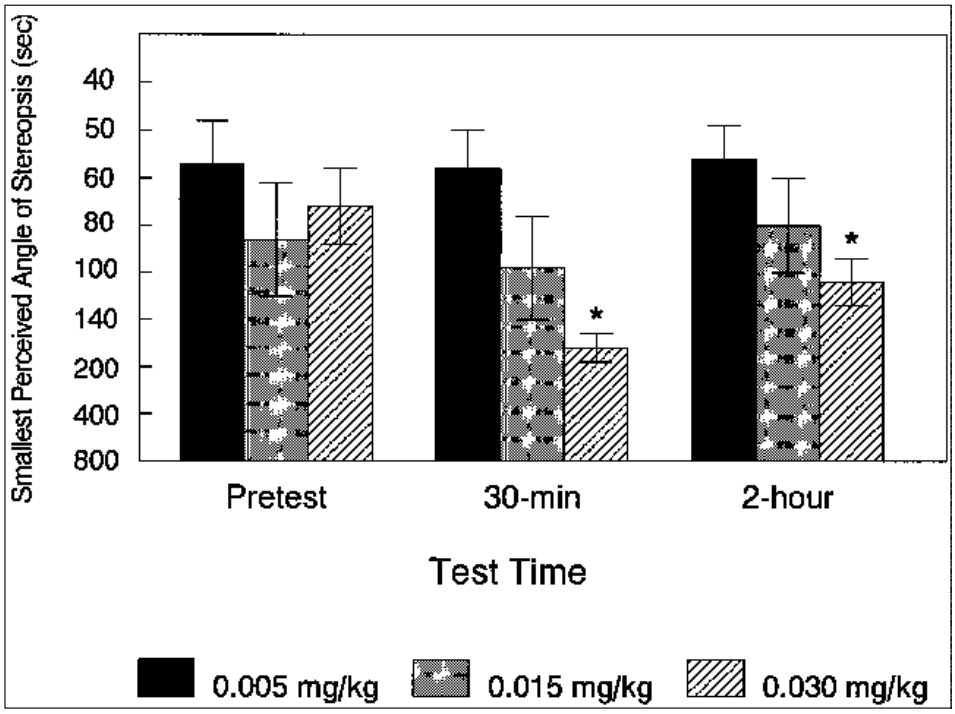

Fig 2. Results of the Circles portion of the stereoscopic depth perception test are depicted. Solid bars represent children assigned to the 0.005 mg/kg triazolam group (n=10). Shaded bars represent children assigned to the 0.015 mg/kg triazolam group (n=10). Stippled bars represent children assigned to the 0.030 mg/kg triazolam group (n=9). Values shown are means ± standard error of the mean. *Indicates a significant change ($p < 0.05$) from pretest stereoscopic depth perception.

triazolam dosages (0.005, 0.015, or 0.030 mg/kg) using the RAND function in Excel® (Microsoft, Redmond, WA). Drug dosages were selected based on suggested triazolam dosages for pediatric patients, and on extrapolations from suggested dosages of midazolam for pediatric patients using triazolam/midazolam equivalence data.[3, 4, 24, 33, 34] Children, parents, and investigators were blinded to the dosage assignment. The children refrained from food and fluids for at least 4 h prior to triazolam administration.

The first vision-testing battery was conducted 30 min following triazolam administration (prior to the dental procedure). The vision-testing battery took approximately 15 min to complete. The memory stimulus for amnesia testing was presented following the first vision-testing battery. A second-vision testing battery was conducted 2 h following triazolam administration (after the dental procedure described below was completed). Tests for amnesia and ataxia (1–2 min each) were completed between the two vision-testing batteries. Pretesting and postsedation side-effects testing were done by the same researcher.

The restorative dental procedure lasted 15–55 min. All treatment procedures were performed by a single operator, who was a second year pediatric dental resident. Neither nitrous oxide nor any restraining device were used. A minimum of one quadrant, which had the highest restorative needs, was operated. Needed extractions were also done. Introduction of instruments such as the anesthetic syringe, rubber dam, and hand piece were standardized using the "tell-show-do" technique. All the children received intraoral injections of 2% lidocaine (30–72 mg) with epinephrine (15–36 µg) beginning 45 min after triazolam administration. No other drugs were administered during the dental procedures. At least one procedure in one quadrant was successfully performed on all children.

Analysis

Each side-effect measure was analyzed separately. Ataxia, amnesia, and the Worth Four-Dot test were analyzed using Cochran-Armitage trend tests, with dose as the independent factor and number of subjects testing positive (for ataxia, amnesia or diplopia) as the dependent factor. If a child failed a test at pretest, his/her postsedation data for that test were not considered in the analyses. Tests for visual acuity and stereopsis were analyzed by ANOVA, with dose (0.005, 0.015, or 0.030 mg/kg) as a between-subject factor and test time (pretest, 30 min, or 120 min after triazolam administration) as a within-subject factor. When ANOVA revealed a main effect of test time, preplanned contrasts were used to assess differences between pretest scores and post-triazolam scores for each of the triazolam doses. The criterion for statistical significance for all tests was $P < 0.05$. ANOVAs and contrasts were performed using Statistica (version 4.5) software (StatSoft, Tulsa, OK). Cochran-Armitage trend tests were performed using Splus statistical software (Statsci, Seattle, WA).

Results

Ataxia. All children had normal gait at pretest. Following triazolam administration, there was a significant increase in the proportion of children who experienced gait ataxia with increasing triazolam dosage ($x^2=8.68$, $P<0.005$). Four of 10, eight of 10 , and 10 of 10 children experienced ataxia in the 0.005, 0.015, and 0.030 mg/kg groups, respectively.

Amnesia. Three children, one in each drug dosage group, failed the amnesia test at pretest. Their post-triazolam data were therefore not included in

the analysis. For the remaining children, there was a significant increase in the proportion of children who experienced anterograde amnesia with increasing triazolam dosage (x^2=3.95, P<0.05). One of nine, three of nine, and five of nine children experienced amnesia in the 0.005, 0.015, and 0.030 mg/kg groups, respectively.

Visual acuity. Visual acuity was moderately decreased in children given 0.030 mg/kg triazolam 30 and 120 min following triazolam administration (6.0±0.0 to 4.3±0.6, F[1, 27]=18.8, P<0.001; from 6.0±0.0 to 5.6±0.2, F[1, 27]=6.97, P<0.02, respectively). No changes in visual acuity were observed with the 0.005 or 0.015 mg/kg doses.

Stereoscopic depth perception. Two children, both in the 0.030-mg/kg dosing group (one at 30 min and one at 120 min), could not be tested on the circles portion of the Vectogram because they were uncooperative. Results for the remaining children on the circles test indicate that 0.030 mg/kg triazolam impaired binocular depth perception (Fig 2). This impairment was observed both 30 and 120 min following triazolam administration (F[1, 24]=12.4, P<0.002, F[1, 24]=7.13, P<0.02). No impairment in depth perception was observed with the 0.005 or 0.015 mg/kg triazolam doses.

Worth Four-Dot. One child in the 0.015 mg/kg group could not perform the Worth Four-Dot test at pretest. This child's data are therefore not included in the analyses. Three additional children (one in the 0.015 mg/kg and two in the 0.030 mg/kg dosing group) could not be tested 30 min after triazolam administration because they were uncooperative. Two of these children (one in the 0.015 and one in the 0.030-mg/kg group) remained uncooperative for testing 120 min following triazolam administration. These data are not included in the analyses. Four additional children (two in the 0.005-mg/kg group, one in the 0.015-mg/kg group, and one in the 0.030-mg/kg group) produced uninterpretable responses on the distance test 30 and/or 120 min following triazolam administration. These responses were also treated as missing data.

Results from the remaining children indicate that the incidence of diplopia increased with increasing doses of triazolam. This effect was evident on the near Worth Four-Dot test at both 30 and 120 min, and on the distance Worth Four-Dot test at 120 min (x^2=4.10, P<0.05, x^2=6.37, P<0.02, x^2=6.51, P<0.02, respectively, Fig 3). In addition, the 30-min Worth Four-Dot distance test revealed a dose-dependent increase in suppression of information from the left eye (reporting two dots, c^2=6.11, P<0.02).

Stability of triazolam in Kool-Aid suspension. The mean (± standard error) amount of triazolam detected in the concentrated suspensions was 0.62 (± 0.14) mg/mL, indicating that the suspension was stable over the week.

Discussion

Triazolam produced dose-dependent ataxia, amnesia, and diplopia in children. The 0.030-mg/kg triazolam dosage also impaired visual acuity and stereoscopic depth perception. Some children appeared to find these side effects upsetting, and it is possible that their occurrence may detract from the efficacy of the drug as an anxiolytic agent. For example, two case reports in the literature describe "psychotic" symptoms, including frightened affect, of children treated for less than one week with benzodiazepines.[35] In both cases, the psychotic symptoms included "visual hallucinations." It is reported that one child had previously experienced such visual hallucinations "secondary to taking an unknown medication for minor dental surgery."[35]

Too few children were tested in this study to draw definitive conclusions regarding the efficacy of each triazolam dosage as a sedative agent. However, in an analogous study, Kaufman and colleagues[36] reported that adult oral-surgery patients receiving 0.50 mg triazolam (0.007 mg/kg, assuming an adult weight of 70 kg) with 50% nitrous oxide experienced a greater incidence of amnesia, a greater impairment in ambulatory function, and were also less cooperative than a group of patients receiving 0.25 mg (0.004 mg/kg, assuming a 70 kg weight) triazolam with 50% nitrous oxide. These investigators note that while drug efficacy measures (anxiety relief, analgesia, patient evaluation of success, etc.) were not dose related, both delayed postoperative recovery and decreased alertness were

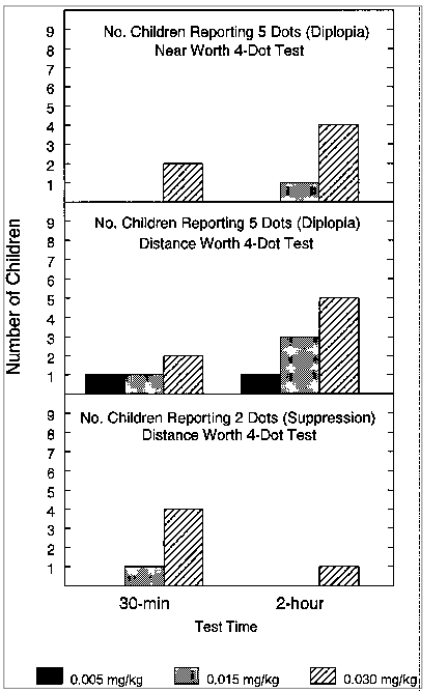

Fig 3. Results of Worth Four-Dot testing.

dose related. Similarly, Silver and colleagues[6] report a nonsignificant trend for 0.3 mg/kg oral midazolam to be more effective than 0.5 mg/kg oral midazolam for sedating physically and neurologically compromised pediatric dental patients. If side effects do detract from triazolam's efficacy, time spent with children beforehand explaining the normal side effects of triazolam might enhance cooperative behavior in children.

A limitation to this study is that we did not include a placebo to control for behavioral difficulties resulting from the dental procedure itself. We had two main reasons for not including a placebo group: 1) the children were referred because they had prior difficulty receiving dental care and parents would have been reluctant to have their children participate if there was a possibility of receiving placebo and 2) this work was conducted as part of a graduate student master's thesis, therefore time constraints prevented the operator from completing more than 30 cases, and adding another operator would have increased variability in the results. Because we did not have a placebo control, we pretested the side-effects measures in all children when they were seen for prophylactic treatment and radiographs on a day prior to the drug trial. Thus the side-effects measures contained a within-subjects control, which allowed us to determine the rate of test failure in the absence of triazolam.

The dose-dependent relationship of the amnestic effects of oral triazolam has been demonstrated in adults.[36, 37] Benzodiazepines are known to affect processing and encoding of information without affecting retrieval of previously learned information.[38] Amnesia is sometimes listed as a benefit, rather than a side-effect of benzodiazepines.[5, 29] It is not unusual for clinicians to use high dosages of benzodiazepines in an attempt to produce amnesia in patients.[39] Although the benefit of amnesia can be debated,[40, 41] the results presented here indicate that clinicians should not rely on the amnestic effects of benzodiazepine medication. The proportion of children who experienced anterograde amnesia was only 56% when the 0.030-mg/kg triazolam dosage was administered.

Blurred vision and loss of visual fusion (resulting in diplopia and loss of stereoscopic depth perception) are known effects of benzodiazepine and other sedative hypnotics.[11, 12] These effects are due to the divergence of the eyes (esophoria or exophoria) after drug administration, and result from a change in muscle tone in the extraocular muscles.[12] These effects have been noted in several studies using high doses of benzodiazepines in adult subjects. For example, in a study of the psychomotor effects of alprazolam (0.25, 0.50, and 1.0 mg) and lorazepam (2.0 mg) in adult subjects, 30% of subjects given 1.0 mg alprazolam and 35% of subjects given 2.0 mg lorazepam reported double vision.[10] Studies with children do not regularly test for such effects. Petti and colleagues[42] report one case of diplopia in nine disturbed children chronically treated with chlordiazepoxide. Roelofse and colleagues[43, 44] have reported nystagmus in children given midazolam (0.35 or 0.45 mg/kg), but these incidents have been rare (one out of 30 and two out of 20, respectively). The findings presented in this manuscript likely reflect an underestimate of the incidence of diplopia, as a number of children in the higher dosages were uncooperative and could not be tested following triazolam administration. Furthermore, the tests used in this study assessed very gross deficits in binocular fusion. A skilled optometrist might have been able to detect more subtle visual disturbances at the lower triazolam dosages.

Children in the 0.030-mg/kg group, but not the 0.005- or 0.015-mg/kg group, had decreased visual acuity when compared with pretest. However, it is not clear that this result is independent of the other effects produced by triazolam. Diplopia in particular may have interfered with the children's ability to recognize the line drawings in the eye chart. Furthermore, the sedative and ataxic effects of triazolam appeared to make it difficult for the children to point properly. Blurred vision has been described as a side effect of some benzodiazepines, however, and this may be a genuine finding.[8]

Uncooperative behavior following benzodiazepine administration has been noted by other investigators.[9] These behavioral effects have been termed "disinhibitory effects." These reactions occur predominantly in younger patients and include extreme upset, anger, and aggressive behavior. It is not clear whether these emotional reactions are due to a direct action of benzodiazepines on emotional centers in the brain, or whether uncooperative behavior results from upset over other benzodiazepine effects such as ataxia and visual disturbances.

In other work, we have found that when 0.025 mg/kg triazolam is given to children in Kool-Aid suspension, plasma triazolam concentrations peak approximately 70 min (range 45 to 128 min) following drug administration.[23] Only minimal clearance of triazolam was observed 120, and even 240 min, following drug administration. (Blood sampling was not carried out beyond 240 min.) Based on these pharmacokinetics, it is not surprising that visual disturbances remained evident at 120 min. Parental reports indicated that the children's vision returned to normal 3.5–12 h following triazolam administration. Clinicians should be aware of the long duration of these side effects when using this class of drugs to control anxiety in children.

Conclusions

1. Triazolam produces ataxia, amnesia, and diplopia in a dose-dependent manner in children.

2. The 0.030-mg/kg triazolam dosage impairs children's visual acuity and stereoscopic depth perception.

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References

1. Fuks AB, Kaufman E, Ram D, Hovav S, Shapira J: Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patients. Pediatr Dent 16:301–305, 1994.
2. Hartgraves PM, Primosch RE: An evaluation of oral and nasal midazolam for pediatric dental sedation. ASDC J Dent Child 61:175–81, 1994.
3. Meyer ML, Mourino AP, Farrington FH: Comparison of triazolam to a chloral hydrate/hydroxyzine combination in the sedation of pediatric dental patients. Pediatr Dent 12:283–87, 1990.
4. Quarnstrom FC, Milgrom P, Moore PA: Experience with triazolam in preschool children. Anesth Pain Control Dent 1:157–59, 1992.
5. Haas DA, Nenniger SA, Yacobi R, Magathan JD, Grad HA, Copp PE, Charendoff MD: A pilot study of the efficacy of oral midazolam for sedation in pediatric dental patients. Anesth Prog 43:1–8, 1996.
6. Silver T, Wilson C, Webb M: Evaluation of two dosages of oral midazolam as a conscious sedation for physically and neurologically compromised pediatric dental patients. Pediatr Dent 16:350–59, 1994.
7. Kozena L, Frantik E, Horvath M: Vigilance impairment after a single dose of benzodiazepines. Psychopharmacology 119:39–45, 1995.
8. Physicians' Desk Reference, 52nd edition. Montvale, NJ: Medical Economics Data Production Co, 1998.
9. Van der Bijl P, Roelofse JA: Disinhibitory reactions to benzodiazepines: A review. JOral Maxillofac Surg 49:519–23, 1991.
10. Vermeeren A, Jackson JL, Muntjewerff ND, Quint PJ, Harrison EM, O'Hanlon JF: Comparison of acute alprazolam (0.25, 0.50 and 1.0 mg) effects versus those of lorazepam 2 mg and placebo on memory in healthy volunteers using laboratory telephone tests. Psychopharmacology 118:1–9, 1995.
11. Brand R, Saunders J, Stewart-Jones J, Richens A: Effect of diazepam on oculomotor balance. Br J Clin Pharmac 1:335–39, 1974.
12. Hannington-Kiff JG: Measurement of recovery from outpatient general anaesthesia with a simple ocular test. Br Med J 18:132–35, 1970.
13. Mattila ME, Mattila MJ, Nuotto E: Caffeine moderately antagonizes the effects of triazolam and zopiclone on the psychomotor performance of healthy subjects. Pharmacol Toxicol 70:286–89, 1992.
14. Iacobucci IL, Archer SM, Giles CL: Children with exotropia responsive to spectacle correction of hyperopia. Am J Ophthalmol 116:79–83, 1993.
15. West CE, Repka MX: A comparison of surgical techniques for the treatment of acquired esotropia with increased accommodative convergence/accommodation ratio. J Pediatr Ophthalmol Strabismus 31:232–37, 1994.
16. Scott WE, Kutschke PJ, Lee WR: 20th annual Frank Costenbader Lecture—adult strabismus. J Pediatr Ophthalmol Strabismus 32:348–52, 1995.
17. Johnson LN: The relative afferent pupillary defect and a novel method of fusion recovery with the Worth 4-dot test. Arch Ophthalmol 114:171–75, 1996.
18. Simons K, Elhatton K: Artifacts in fusion and steropsis testing based on red/green dichoptic image separation. J Pediatr Ophthalmol Strabismus 31:290–97, 1994.
19. Lueder GT, Arnoldi K: Does "Touching Four" on the Worth 4-dot test indicate fusion in young children? A computer simulation. Opthalmology 103:1237–40, 1996.
20. Birch E, Williams C, Hunter J, Lapa MC: Random dot stereoacuity of preschool children. ALSPAC "Children in Focus" Study Team. J Pediatr Ophthalmol Strabismus 34:217–22, 1997.
21. Creedon RL: Pharmacological management of patient behavior. In Dentistry for the Child and Adolescent, 6th Ed. McDonald RE, Avery DR, eds, St. Louis: Mosby, 1994, pp 307–334.
22. Quarnstrom FC, Milgrom, P, Moore PA: Experience with triazolam in preschool children. Anesth Pain Control Dent 1:157–59, 1992.
23. Karl HW, Milgrom P, Domoto P, Kharasch ED, Coldwell SE, Weinstein P, Leroux B, Awamura K, Mautz D: Pharmacokinetics of oral triazolam in children. J Clin Psychopharmacol 17:169–72, 1997.
24. Berthold CW, Schneider A, Dionne RA: Using triazolam to reduce dental anxiety. J Am Dent Assoc 124:58–64, 1993.
25. Hartgraves PM, Primosch RE: An evaluation of oral and nasal midazolam for pediatric dental sedation. ASDC J Dent Child 61:175–81, 1994.
26. Krafft TC, Kramer N, Kunzelmann KH, Hickel R. Experience with midazolam as a sedative in the dental treatment of uncooperative children. ASDC J Dent Child 60:295–99,1993..
27. American Academy of Pediatric Dentistry. Guidelines for the elective use of pharmacologic conscious sedation and deep sedation in pediatric dental patients. Pediatr Dent 19: 48-52, 1997.
28. Glick TR. Neurologic Skills: Examination and Diagnosis. Boston: Blackwell Scientific Publications, 1993.
29. Flaitz CM, Nowak AJ, Hicks MJ: Evaluation of the anterograde amnesic effect of rectally administered diazepam in the sedated pedodontic patient. ASDC J Dent Child 53:17–20, 1986.
30. Fern KD, Manny RE: Visual acuity of the preschool child: a review. Am J Optom Physiol Opt; 63:319–45, 1986.
31. Somers WW, Hamilton, MJ: Estimation of the stereoscopic threshold utilizing perceived dept. Ophthal Physiol Opt 4:245–50, 1984.
32. Worth C: Squint: Its Causes. Pathology and Treatment. 4th ed. Philadelphia, PA: Blakiston's Sons & Co 14, 1915.
33. Kupietzky A, Houpt MI: Midazolam: a review of its use for conscious sedation of children. Pediatr Dent 15:237–41, 1993.
34. Sostmann HJ, Sostmann H, Crevoisier C, Bircher J: Dose equivalence of midazolam and triazolam: A psychometric study based on flicker sensitivity reaction time and digit symbol substitution test. Eur J Clin Pharmacol 36:181–87, 1989.
35. Pfefferbaum B, Butler PM, Mullins D, Copeland DR: Two cases of benzodiazepine toxicity in children. J Clin Psychiatry 48:450–52, 1987.

36. Kaufman E, Hargreaves KM, Dionne RA: Comparison of oral triazolam and nitrous oxide with placebo and intravenous diazepam for outpatient premedication. Oral Surg Oral Med Oral Pathol 75:156–64, 1993.
37. Kirk T, Roache JD, Griffiths RR: Dose-response evaluation of the amnestic effects of triazolam and pentobarbital in normal subjects. J Clin Psychopharmacol 10:160–67, 1990.
38. Mewaldt SP, Hinrichs JV, Ghoneim MM: Diazepam and memory: support for a duplex model of memory. Mem Cognit 11:557–64, 1983.
39. Kurzrock M: Triazolam and Dental Anxiety (letter). J Am Dent Assoc 125: 358, 360,1994.
40. Coldwell SE, Milgrom P, Getz T, Ramsay DS: Amnestic and anxiolytic effects of alprazolam in oral surgery patients. J Oral Maxillofac Surg 55:1061–70, 1997.
41. File SE, Easton P, Skelly AM: Amnesia for dental procedures and mood change following treatment with nitrous oxide or midazolam. Int Clin Psychopharmacol 6:169–78, 1991.
42. Petti TA, Fish B, Shapiro T, Cohen IL, Campbell M: Effect of chlordiazepoxide in disturbed children: a pilot study. J Clin Psychopharm 2:270–73, 1982.
43. Roelofse JA, Van der Bijl P, Stegmann, DH, Hartshorne JE: Preanesthetic medication with rectal midazolam in children undergoing dental extractions. J Oral Maxillofac Surg 48:791–96, 1990.
44. Roelofse JA, Van der Bijl P: Comparison of rectal midazolam and diazepam for premedication in pediatric dental patients. J Oral Maxillofac Surg 51:525–29, 1993.