Recovery Following Sedation with Midazolam or Diazepam Alone or in Combination with Fentanyl for Outpatient Surgery

Mark W. Ochs,[1] D.M.D., Myron R. Tucker,[1] D.D.S., Raymond P. White,[1] Jr., D.D.S., Ph.D., Jay A. Anderson,[1,2] D.D.S., M.D.

Oral and Maxillofacial Surgery[1] and Department of Anesthesiology[2] University of North Carolina, Chapel Hill, N.C.

Summary

Midazolam is a new water-soluble benzodiazepine with a much shorter pharmacologic half-life than diazepam. Despite this shorter pharmacologic half-life, several reports indicate that patients do not recover more rapidly after sedation with midazolam than with diazepam. The purpose of this study was to compare recovery of patients sedated with either midazolam or diazepam alone or in combination with fentanyl using the digit symbol substitution test (DSST) and Trieger test. Patients were randomly divided into treatment groups and recovery tests were administered to the patients prior to sedation and at 60, 120, and 180 minutes after achieving a standardized sedative endpoint. Patients who received midazolam alone had significantly fewer numbers of correct reponses on the DSST than patients who received midazolam plus fentanyl or diazepam with or without fentanyl. When midazolam was combined with fentanyl there was no significant difference between results obtained on the DSST when compared with either diazepam group. Comparisons between all groups using dots missed or millimeter deviation on the Trieger test showed no statistical difference between any groups. These data indicate that midazolam as a single IV agent has a slightly prolonged recovery phase compared to diazepam. The addition of fentanyl to the sedation regimen allows reduction in the midazolam dose resulting in a recovery time comparable to that of diazepam.

Introduction

Intravenous diazepam is widely used for conscious sedation in both ambulatory and inpatient procedures. A short-acting narcotic such as fentanyl is often administered with diazepam to provide analgesia and supplement the sedative effect. Midazolam, a new water-soluble benzodiazepine, is prepared as a hydrochloride or maleate salt and buffered to a pH of approximately 3.5. In its parenteral solution, which contains no propylene glycol, the diazepine ring is open. After injection, the higher plasma pH of 7.4 causes ring closure with an increase in lipophilicity;[1,2] the presumed reason for its rapid onset of action which is reported to be as rapid as 15-89 seconds when administered IV.[3-5] Midazolam has a distribution half-life ($T_{½\alpha}$) of 15 minutes and an elimination half-life ($T_{½\beta}$) of approximately 2.5 hours.[6] This compares to diazepam's $T_{½\alpha}$ of 30-60 minutes and $T_{½\beta}$ of greater than 24 hours.[7] Midazolam is metabolized via hydroxylation by hepatic microsomal oxidative enzymes.

Initial studies have shown the advantages of midazolam include less incidence of thrombophlebitis and a greater level of amnesia compared to diazepam.[8,9] Dental outpatients who received midazolam (0.1 mg/kg) had more complete amnesia of intraoperative events than those who had received diazepam (0.2 mg/kg). Despite the more rapid clearance and lower plasma levels of midazolam, shorter clinical recovery rates have not been demonstrated. In one study, patients' ability to stand and walk steadily returned to normal more slowly in patients given midazolam (0.1 mg/kg) compared with those who received diazepam (0.2 mg/kg) IV. In the same study three psychomotor paper-and-pencil tests administered as a baseline compared to a 2 hour post sedative test showed no difference between groups.[10]

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Address correspondence to Dr. Myron Tucker, Dept. of Oral and Maxillofacial Surgery, School of Dentistry, The University of North Carolina, Chapel Hill, NC 27514.

It is difficult to compare recovery from psychoactive drugs and to correlate this to "street fitness" or discharge criteria. The abundance of psychomotor tests used to assess drug impairment are often elaborate, time consuming, impractical, or expensive. Pure sensory testing (such as auditory threshold or eyelid responses) are unreliable measures of a drug's central effects.[11] Two simple paper-and-pencil tests that have been widely used and shown to be effective in evaluating recovery are the Trieger test[12,13] and digit symbol substitution test (DSST).[11,14]

The objective of this study was to assess the recovery from intravenous sedation comparing patients sedated with midazolam or diazepam alone or in combination with fentanyl.

Materials and Methods

A total of 80 patients scheduled for outpatient third molar removal were entered into this double blind parallel group study. All patients were American Society of Anesthesiology Physical Status I or II patients. Upon entry into this study, patients were randomly assigned to receive 1 of 4 possible treatment combinations, including midazolam and saline (M), midazolam and fentanyl, (MF), diazepam and saline (D), or diazepam and fentanyl (DF). Prior to the start of the procedure, the patient was acclimated to the study environment and baseline vital signs were recorded. Blood pressure and pulse rate were recorded using an automatic blood pressure monitoring system with hard copy capability. Respiration was carefully monitored by visual inspection. A baseline Trieger test and DSST were then administered. Following completion of these tests, an intravenous (IV) catheter was inserted for continuous IV drip with 5% dextrose in 0.45% normal saline and the sedative agents were administered IV by the anesthetist.

Normal saline (.03 ml/kg) or fentanyl (.03 ml/kg, .05 mg/ml) was given at a rate of 1 ml/min. Five minutes following administration of the saline or fentanyl, midazolam (5 mg/ml) or diazepam (5 mg/ml) was administered at a rate of 0.5 ml/min. The sedative endpoint (SEP) was reached when the patient's speech became thickened and slurred and Verrill's sign (ptosis) was evident. This was determined by the operating surgeon who was blind to the sedative agent. Immediately after the SEP was reached, local anesthesia (2% lidocaine with 1:100,000 epinephrine) was administered and the surgical procedure was begun. If the operating surgeon determined the level of sedation was inadequate, an additional maintenance sedative dose (25% of the initial sedative endpoint dose) was administered during the procedure. Vital signs were recorded at 1 minute intervals until the sedative endpoint (SEP) had been reached and 5 minute intervals from SEP to the completion of sedation.

Following the completion of the surgical procedure, the patient was transferred to a recovery room and vital signs, the Trieger test, and DSST were repeated at 60, 120, and 180 minutes from the time of sedative endpoint.

The DSST was evaluated by determining the number of correct responses completed at each interval. The Trieger test was evaluated by determining the number of dots missed as well as the total millimeters of deviation on this test for each of the pre and postoperative intervals. Analysis of covariance and comparisons of treatments with regard to the DSST and Trieger tests were performed. Results were then tested using a two-sided T-test with p value set at .05. Analysis of variance was also used to analyze the initial sedation dose and time to sedative endpoint for each group. With respect to initial sedation dose, comparisons were limited to M versus MF and D versus DF. With respect to time to sedative endpoint, all possible comparisons between the four treatment groups were performed. All comparisons were two-sided.

Results

There were no intraoperative or postoperative complications associated with administration of the drugs in this study. All 80 patients completed all aspects of preoperative and postoperative testing. The means and ranges with regard to initial and total doses and time to sedative endpoint parameters for each group are shown in Table 1. Both the M and the MF groups had a significantly shorter average time to sedative endpoint than patients receiving D or DF ($p < .01$). Patients receiving DF required a significantly ($p < .01$) lower average dose of diazepam to reach the sedative endpoint than patients receiving D.

Results of correctly matched pairs on the DSST are shown in Table 2. The analysis of covariance with respect to DSST results indicated that a significant difference existed among treatment groups at all three observation points. Patients receiving midazolam alone had a significantly lower average number of correctly matched pairs on the DSST than all other groups at 60 minutes ($p < .001$) and 120 minutes ($p < .05$). The M group also had a significantly lower average number of correctly matched pairs than both diazepam groups at 180 minutes post sedative endpoint ($p < .05$). At this time both diazepam groups had slightly exceeded their baseline scores and the MF group had achieved 98% of their baseline testing.

The results of Trieger test dots missed are shown in Table 3A and the millimeter deviation comparisons are shown in Table 3B. There were no statistically significant differences between treatment groups with respect to the Trieger test. At 180 minutes post sedative endpoint, all groups failed to return to baseline values for number of dots missed and millimeters of deviation in the Trieger test.

TABLE 1 Mean Doses (I standard Deviation) and Time to Sedative Endpoint

	M	MF	D	DF
Initial sedation Dose (mg/kg)	.17(±.06)	.12(±.04)	.35(±.14)	.26(±.12)
Maintenance sedation Dose (mg/kg)	.04(±.03)	.01(±.02)	.09(±.09)	.06(±.06)
Total sedation Dose (mg/kg)	.21(±.09)	.13(±.05)	.45(±.14)	.32(±.13)
Time to sedative Endpoint (min)	3.80(±1.1)	2.40(±1.1)	7.80(±3.3)	6.50(±3.6)

TABLE 2 Psychomotor recovery over time as measured by the DSST (number of correctly matched pairs).

Treatment Group	n	Baseline	60 min	120 min	180 min
Midazolam	20	59.5	37.5[1]	43.0[2,3]	52.6[4,5]
Midazolam + fentanyl	20	55.9	45.5	50.6	55.0
Diazepam	20	56.5	47.2	49.9	56.9
Diazepam + fentanyl	20	57.7	49.2	51.3	58.5

Significant difference for pair wise comparison (two-sided t-test:
[1]$p < .01$ compared to other three groups
[2]$p < .01$ compared to MF and DF
[3]$p < .05$ compared to D
[4]$p < .01$ compared to DF
[5]$p < .01$ compared to D

TABLE 3 Psychomotor recovery over time as measured by Trieger Test

A Mean number of dots missed

Treatment Group	n	Baseline	60 Mins.	120 Mins.	180 Mins.
Midazolam	20	2.3	9.6	7.3	6.0
Midazolam + fentanyl	20	2.2	8.5	5.5	4.5
Diazepam	20	2.1	10.1	7.2	7.3
Diazepam + fentanyl	20	2.6	8.2	7.6	4.9

B. Total mm deviation

Treatment Group	n	Baseline	10 Mins.	120 Mins.	180 Mins.
Midazolam	20	2.3	12.0	8.3	6.8
Midazolam + fentanyl	20	2.2	9.4	5.8	4.7
Diazepam	20	2.1	11.2	7.7	7.5
Diazepam + fentanyl	20	2.6	8.8	8.0	5.2

Discussion

The Trieger test is a modification of a single Bender Motor Gestalt test solid line form.[12] Dots spaced approximately 12 mm apart are connected by the patient to recreate the figure. Reception of visual stimuli causing an appropriate coordinated motor response is tested and quantified. Newman, *et al.* showed the Trieger test to be an effective measure of recovery from anesthesia.[12]

In our study the Trieger test failed to demonstrate any significant difference in recovery rates among the drug combinations tested. Several other studies utilizing the Trieger test[15,16] and other psychomotor testing[8,17,18] have found similar recovery rates for midazolam and diazepam when given in equipotent IV doses. In this study all groups failed to reach their baseline scores in the final Trieger test. Similar results have been reported in other studies as well.[10,12,13,15] Results may be attributed to fatigue and

psychological stress of surgery which may exaggerate any psychomotor dysfunction. In one study patients receiving only local anesthesia for dental surgery performed below baseline levels at the end of the recovery period.[13] This demonstrates that absolute scores are not accurate indicators of recovery. We administered all tests in the same semi-supine position to eliminate any effect that position changes may have on sequential test performances. Gelfman, *et al.* found the perceptual speed test (a one minute test similar to the DSST) to be more sensitive than the Trieger test in assessing differences between anesthetic groups.[19]

The DSST is a timed test (45 seconds) which probably requires a higher level of cognitive association. This test involves the recognition and association of two separate elements requiring higher mental coding processes. The observed drug effects are not a result just of impaired visual or sensory function. The principle determinant of performance is the recoding of visual information.[11] Other possible contributing factors are disturbance of central motor coordination, short-term memory, and peripheral muscle relaxation.[14] The sample section of the DSST trains and orients the patient to the tasks involved. It is important that the digit-symbol pairing be modified on repeated administrations so that patients are not able to remember the digit-symbol code and increase their performance.[11] This helps eliminate the higher performance through "practice and learning" which may interfere with sequential testing comparisons and may make the DSST a more valid test of recovery than the Trieger test, which is subject to a practice effect with repeated testing.

Midazolam has a short half-life of elimination ($T_{½\beta}$) between 1.7 and 2.4 hours[20,21] compared with diazepam's $T_{½\beta}$ of greater than 24 hours.[7] In cats the disappearance of benzodiazepines from plasma and CSF (directly sampled from the cisterna magna) occurred in parallel. The half-lives for the two compartments were highly correlated ($r=0.85$, $p < .01$). Entry of benzodiazepines into a protein-free body compartment such as CSF is by passive diffusion and is in equilibrium with the unbound drug in the plasma.[22] Both midazolam and diazepam are highly protein bound and are relatively lipid soluble with similar volumes of distribution (diazepam 0.7-1.7 l/kg, midazolam 1.1-1.7 l/kg).[23] At equilibrium, midazolam and diazepam have comparable CSF/plasma concentration ratios, 0.12 and 0.14 respectively.[22] There is a significant correlation between plasma concentration of midazolam and psychologic performance testing ($r=0.68$-0.92).[21] Therefore, one would expect midazolam's central effects to terminate sooner than diazepam's since midazolam is cleared from the peripheral compartments faster.

Our results are in agreement with other recent clinical studies which found that midazlam's rapid disappearance from the blood is not associated with rapid recovery, a finding thus far unexplained by pharmacokinetics or metabolism studies. Midazolam is extensively metabolized in the liver with less than 0.03% excreted unchanged in the urine. In contrast to diazepam, hepatic clearance of midazolam is nonrestrictive. Liver microsomal enzymes may degrade both the bound and free drug.[21] Midazolam's main metabolite is α - hydroxymidazolam (1-hydroxymethylmidazolam) which has a very short elimination half-life ($T_{½\beta} < 1H.$) because of its rapid conjugation in the liver and subsequent elimination by the kidney as a glucuronide. (See Fig. 1) This metabolite is weak pharmacologically (approximately one tenth as potent as midazolam) and the amount formed after IV administration of midazolam (0.15 mg/kg) adds little to psychomotor impairment.[24] The metabolite plays a much more important role after an oral dose of midazolam, with more being formed in the high (up to 60%) first pass metabolism of the parent drug.[20] Thus, α - hydroxymidazolam may intensify IV midazolam's effects but should not prolong them.

Crevoisier, *et al.* found the minimal effective plasma concentration to be 30-100 ng/ml using reaction time and tracing tests.[24] Similar values of 40-80 ng/ml were found in another study.[21] Midazolam plasma levels obtained within several hours after sedation of dental patients with midazolam (0.1 mg/kg) IV showed no drug present in 5 of 18 patients. The remaining 13 patients' drug levels range from 5 to 61 ng/ml with an average of 21.4 ng/ml. In another study, sequential plasma levels of midazolam were drawn following IV administration of midazolam (0.15 ng/kg). Mean midazolam levels of 84.2 and 49.5 ng/ml were found at 2 and 3 hours post injection respectively.[25]

While midazolam is cleared more rapidly, it appears that sufficient plasma concentrations exist to cause psychomotor impairment in the time period we studied. Using the DSST, the M group had a prolonged recovery time while the MF group showed no

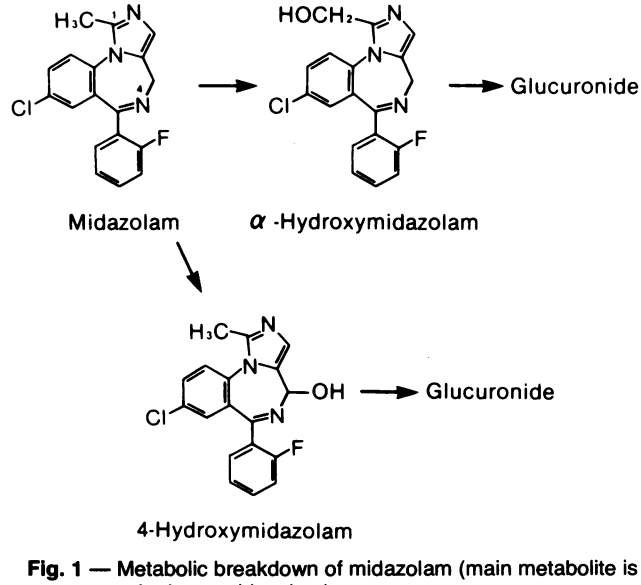

Fig. 1 — Metabolic breakdown of midazolam (main metabolite is α-hydroxy-midazolam).

significant differences in recovery rates when compared with either diazepam group. The decreased recovery rates of the MF group when compared to the M group appear to be a function of the reduction of midazolam dose when fentanyl is administered, thereby reducing the level of psychomotor impairment attributed to midazolam. Thus, with the addition of a narcotic, the associated increased risk of respiratory depression must be weighed against the benefit of decreased recovery time.

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