A randomized comparison of midazolam and diazepam injectable emulsion in cataract surgery

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The purpose of this study was to compare the psychomotor recovery of patients sedated with either midazolam or Diazemuls using the digit symbol substitution test and the Trieger test. Sixty patients were allocated in random double-blind fashion to receive either midazolam or diazepam in oil emulsion (Diazemuls) as intravenous sedation for cataract surgery. Both groups received fentanyl 0.5 $\mu g \cdot kg^{-1}$ IV. Tests of cognition were performed by the patients prior to sedation and at half-hourly intervals for three hours after cataract surgery. In a dose ratio of 1:4, midazolam was found to produce better sedation but more prolonged recovery than Diazemuls. Anterograde amnesia was comparable in the two groups, while more patients in the Diazemuls group developed episodes of apnoea and venous irritation.

Le but de cette étude est de comparer le réveil psychomoteur des patients sédationnés avec soit du midazolam soit du Diazemuls utilisant les tests de « The digit symbol substitution » et celui de «Trieger». Soixante patients ont été divisés au hasard et à double insu afin de recevoir soit du midazolam, soit du diazépam dans un émulsion huileuse (Diazemuls) pour une sédation intraveineuse pour une chirurgie de cataracte. Les deux groupes ont reçu du fentanyl 0,5 $\mu g \cdot kg^{-1}$. Les tests ont été faits par les patients avant la sédation et à des intervalles de 30 minutes pour trois heures après la chirurgie de cataracte. Dans le rapport de dose de 1:4, le midazolam a été trouvé comme fournissant une meilleure sédation et un réveil plus prolongé que le Diazemuls. L'amnésie antérograde était comparable dans les deux groupes, alors qu'un nombre plus élevé de patients dans le groupe Diazemuls a développé des épisodes d'apnée et une irritation veineuse.

Key Words
HYPNOTICS: benzodiazepines, midazolam, diazepam; ANAESTHESIA: ophthalmological.

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Cataract extraction is frequently performed as day-case surgery under neuroleptic anaesthesia to supplement retrobulbar regional block. The usual anaesthetic regimens include a combination of intravenous fentanyl and diazepam. Most patients for cataract extraction are elderly with multiple concurrent medical disorders. With the decrease in systemic functional reserve and possibility of drug interactions in geriatric patients, they may be more susceptible to delayed mental recovery[1] and cardiovascular or respiratory depression[2] after sedation.

Midazolam has been reported to have better anterograde amnesia, shorter elimination half-life, and a relatively faster recovery than diazepam;[3] it may be a better choice for sedation in this elderly outpatient setting. The purpose of this study was to compare the side-effects and effectiveness of intravenous midazolam and diazepam injectable emulsion as supplements to fentanyl neuroleptic anaesthesia in patients undergoing cataract surgery with retrobulbar block.

Methods

This study was approved by the Hospital Ethics Committee. Informed consent was obtained from 60 ASA physical status I–II outpatients aged 55 yr or more who were scheduled for elective cataract extraction with retrobulbar block and intravenous sedation. Patients with known or suspected allergy to benzodiazepines, emulsion, fentanyl, or clinically significant systemic diseases, those already receiving psychotropic medications or suffering from impaired mental function and those unable to function or read with the unoperated eye were excluded. Demographic, medical, surgical, and social histories along with medications used were recorded. The patients' ability to read with the unoperated eye was confirmed.

Patients received no premedication. Intraoperatively

they were monitored with an ECG, automatic BP cuff, pulse oximeter, and mass spectrometer for respiratory rate. Supplemental oxygen by a face mask was administered. All patients received fentanyl 0.5 $\mu g \cdot kg^{-1}$ IV, and were then randomly allocated to receive either midazolam (Versed) or diazepam in a lipid emulsion (Diazemuls) by slow IV injection over one to three minutes as intraoperative sedation prior to the retrobulbar block. Midazolam was administered at an initial dose of 0.015 $mg \cdot kg^{-1}$ while Diazemuls was administered at an initial dose of 0.06 $mg \cdot kg^{-1}$. The sedative end-point was defined and considered to have been reached, by the anaesthetist, when the patient was comfortable, calm and relaxed, and did not object to the retrobulbar block nor the surgical proceeding. Both the investigator doing the psychomotor evaluations and the patients were double-blinded as to the type of sedative given by masking both the syringe and IV tubing.

If necessary, additional maintenance doses of either medication were given in increments of 25 per cent of the initial dose to maintain the desired level of sedation before and during the cataract surgical procedure. Other medications such as antihypertensives were given when considered necessary and such supplementary medications were recorded.

Heart rate, systolic and diastolic blood pressure and the respiratory rate were measured preoperatively, before intravenous sedation, at 5, 10, 15, 30 and 60 min after the sedative end-point, at the end of the procedure and prior to discharge from the hospital.

Psychomotor tests

Trieger test

The Trieger test is a reliable and reproducible index of performance in successive trials, measuring sensory motor performance, a critical determinant of recovery. It is a simple, direct, self-administered objective test to measure recovery time using a test sheet that consists of a figure conforming to the Bender-Gestalt solid line form but having the solid line replaced by dots 12–13 mm apart. The patient is required to connect the dots as accurately as possible to complete the shape. The number of dots missed and the deviation in millimeters are evaluated to produce two scores for each test. A positive correlation between the degree of error and length of recovery time of >0.55 makes this test a valuable index of recovery from anaesthesia.[4]

Digit symbol substitution test (DSST)

This test is sensitive to central nervous system disruption,[5] and requires the patient to integrate visual scanning speed with substitution of numbers for symbols at maximal speed combined with accuracy. It is well adapted to bedside administration. The patient is allowed 90 sec to complete as many of the 110 symbols to number substitutions as possible, using a code provided at the top of the page containing the test items. Both the total number of substitutions completed and the number completed correctly are evaluated to produce two scores for the test. A sensitivity of 86 per cent using a cutoff point 1.5 standard deviations (SD) below the mean for a variety of age groups[6] has been reported.

Patients were evaluated prior to sedation and surgery using both psychomotor tests to provide baseline measures of their cognitive skills and to exclude any individuals with dementia. Both tests were readministered 30, 60, 90, 120, and 180 min after surgery using alternative forms of the Digit Symbol Substitution Test to offset practice effects. The state of consciousness was scored on a scale of 0 to 4, with 0 = awake, 1 = slightly drowsy, 2 = moderately drowsy, 3 = markedly drowsy, 4 = not arousable. Such scoring was done at five and ten minutes after the sedative end-point, at the end of the surgical procedure and at 30 min after surgery. Patients were shown a sample picture of a familiar object at the sedative end-point and asked to remember it. Postoperatively, at 1 and 24 hr, they were asked the identity of the picture to test anterograde amnesia. The orientation of the patient to time and place was assessed preoperatively, at 60 min after the sedative end-point, at the end of surgery and at 30, 60, 90, 120 and 180 min after surgery. The degree of orientation was rated according to the following scale; 0 = fully oriented, 1 = partially oriented, 2 = fully disoriented.

The intravenous site was examined at one hour after surgery for evidence of tenderness, pain under pressure, swelling, burning or other untoward effects. A 24 hr follow-up inquiry by phone for similar problems was undertaken.

Data are presented as means ± SEM. Subjective measures and anterograde amnesia tests were evaluated by chi-square analysis. The DSST was evaluated by determining the number of correct responses on each test. The Trieger test was analyzed by determining the number of dots missed as well as the total deviation in millimeters for each of the pre- and postoperative tests. All the psychomotor testing was performed with patients in the semi-reclining positions and using reading spectacles. Analysis of covariance and comparison of treatments with regard to the DSST and Trieger tests were performed. Results were then tested using a two-sided t test. $P < 0.05$ was considered statistically significant.

Results

There were 31 patients in the midazolam group and 29 in

TABLE I Demographic data

	Midazolam $n = 31$	*Diazemuls* $n = 29$
Age (yr)	69.6 ± 7.0	70.9 ± 6.4
Weight (kg)	68.0 ± 14.2	67.1 ± 11.4
Sex	M:11 F:20	M:14 F:15
ASA status	I:11 II:20	I:10 II:19

Mean ± SEM.

TABLE II Intraoperative medications

	Midazolam	*Diazemuls*
Fentanyl (μg)	35.1 ± 8.0	35.7 ± 10.3
Midazolam (mg)	1.17 ± 0.33	—
Diazemuls (mg)	—	4.50 ± 1.17
Dose (mg · kg^{-1})	0.02 ± 0.005	0.07 ± 0.01

the Diazemuls group, their mean ages were 69.6 ± 1.3 and 70.9 ± 1.2 yr respectively. The demographic data are shown in Table I. No significant differences were noted between the two groups with regard to their weight, sex, smoking habits, alcohol consumption, ASA classification, or duration of surgery. No differences were found in their past medical history or the type and quantity of daily medications consumed.

None of the patients received any premedication. Both groups received similar amounts of fentanyl (midazolam vs Diazemuls, 35.1 ± 8.0 vs 35.7 ± 10.3 μg). One group received a mean total dose of 1.17 ± 0.06 mg (0.02 mg · kg^{-1}) of midazolam and the other a mean total dose of 4.5 ± 0.22 mg (0.07 mg · kg^{-1}) of Diazemuls (Table II).

The heart rate ten minutes after the sedative end-point was significantly different (midazolam vs Diazemuls, 63.2 ± 1.8 vs 70.0 ± 2.6; beats · min^{-1} $P < 0.05$). Heart rate measured at the other time periods showed no significant differences even though a trend towards higher rates was noted in the Diazemuls group. Mean arterial blood pressure, respiratory rate and oxygen saturation were not significantly different between drugs at any of the time periods.

Five patients developed episodes of apnoea intraoperatively as detected by the apnoeic alarm on mass spectrometry, one from the midazolam group and four from the Diazemuls group. A patient was considered apnoeic if no breaths were detected for a period longer than 15 sec. The number of episodes ranged from one to ten and usually occurred within the first 15 min after the sedative end-point. Oxygen saturation was not significantly decreased at any point during the periods of apnoea.

The degree of sedation after the sedative end-point showed significant differences between drugs at five and

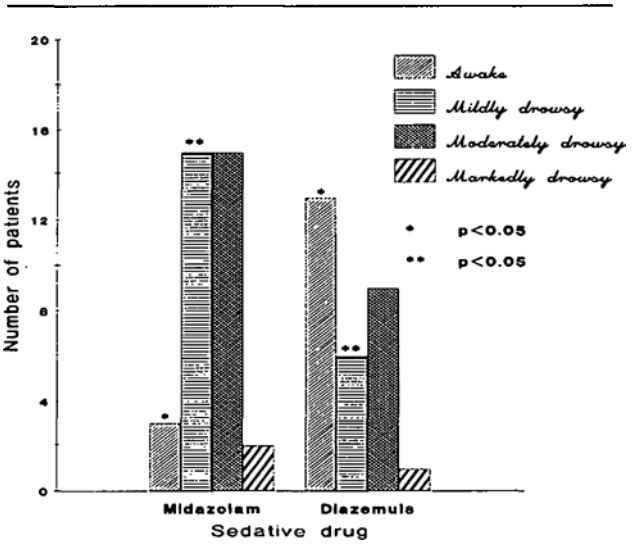

FIGURE 1 A comparison of the degree of sedation at 10 min after the sedative end-point. * and ** indicate a difference between groups.

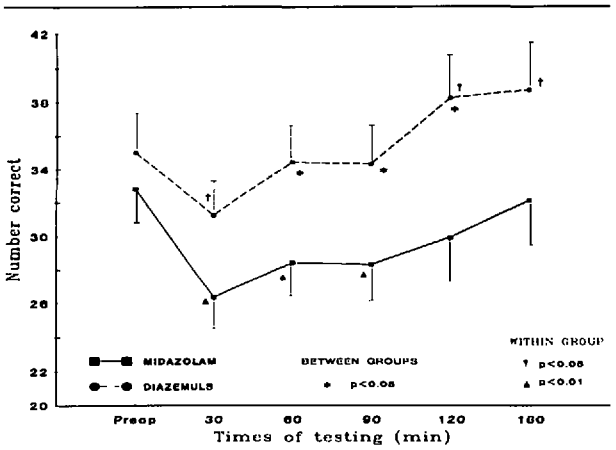

FIGURE 2 A comparison of the scores obtained in the digit symbol substitution test in the drug groups (mean ± SEM). Differences between and within the two groups are shown.

ten minutes between the two groups. Patients who received midazolam were more drowsy than those who received Diazemuls (Figure 1). No differences in sedation were noted between the two drugs at the end of surgery or at 30 minutes post-surgery, and no differences were noted over time or between drug groups with respect to the orientation of patients.

The results of the Digit Symbol Substitution Test showed significant changes both between and within the drug groups (Figure 2). In the Diazemuls group, the performance returned to baseline at 60 min, and was significantly improved over baseline at 120 and 180 min. The deterioration persisted at 90 min in the midazolam

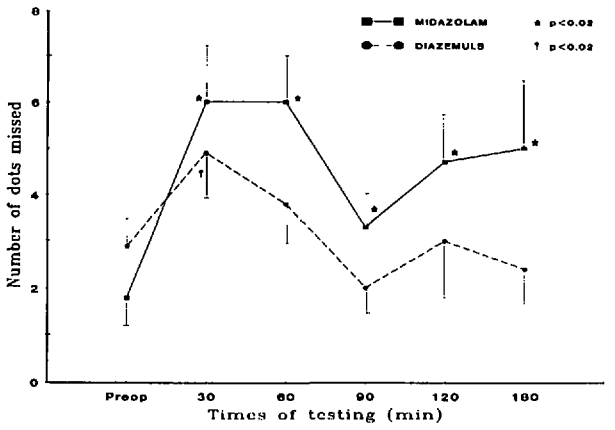

FIGURE 3 A comparison of the number of the dots missed in the Trieger test with baseline (mean ± SEM). * and + indicate a postoperative within group deterioration.

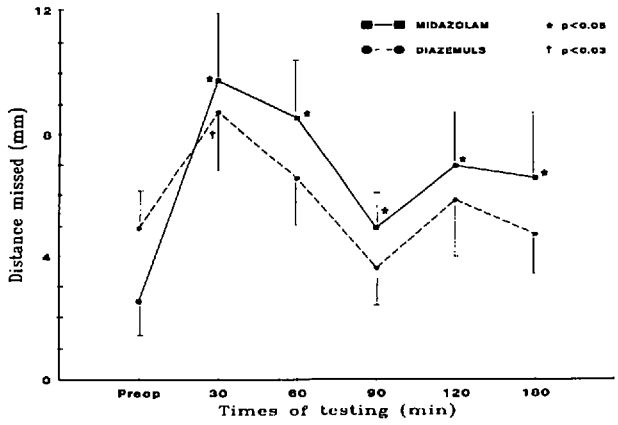

FIGURE 4 A comparison of the cumulative deviation in the Trieger test in millimeters with baseline (mean ± SEM). * and + indicate a postoperative deterioration within groups.

group, returning to baseline only at 120 and 180 min (Figure 2).

The Trieger test, both in the number of dots missed and the deviation in millimeters (Figures 3 and 4) did not show any significant differences between the midazolam or Diazemuls groups at any of the time periods tested. However, a postoperative increase in the number of dots missed and the deviation in millimeters were noted at 30 min in each group when compared with its respective baseline preoperative value. These changes persisted for 180 min in the midazolam group whereas in the Diazemuls group, the difference was noted only at 30 min, having returned to baseline levels by 60 min.

Five patients in the Diazemuls group complained of mild tenderness at the injection site at one and 24 hr

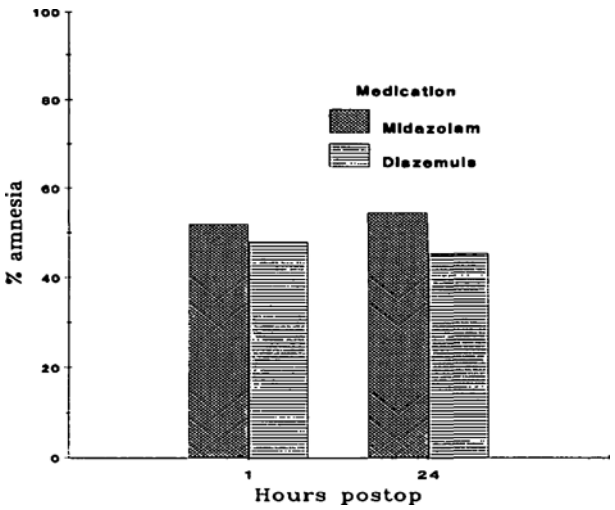

FIGURE 5 A comparison of the extent of postoperative amnesia at 1 and 24 hrs in the two drug groups.

assessments whereas none in the midazolam group experienced any problems ($P < 0.01$). Although at 1 and 24 hr after surgery, anterograde amnesia was not significantly different between the two groups (Figure 5), a higher percentage of patients had amnesia in the midazolam group (55 per cent) when compared with the Diazemuls group (45 per cent).

Discussion

The ideal drug for outpatient cataract extractions should have a rapid onset of action, last for a short time and provide optimal relaxation. In this study, midazolam, a water soluble benzodiazepine, was compared with Diazemuls for sedation during outpatient cataract surgery in a randomized double-blind trial. Diazemuls is an oil-in-water emulsion with diazepam dissolved in the oleaginous phase. Therapeutically, it has been found to be as effective as "aqueous" solutions of diazepam with an extremely low incidence of local side-effects.[7] While some studies have shown similar or quicker recovery with midazolam than with diazepam,[8–11] others have not.[12–15] We found that the early recovery was significantly slower following midazolam than Diazemuls as assessed by tests requiring mental concentration.

After intravenous benzodiazepine, the initial phase of rapid disappearance is due to distribution of the drug with the slower phase of disappearance due to biotransformation. Both midazolam and diazemuls are equivalently lipophilic and consequently have similar volumes of distribution which determines the duration of action and initial recovery. The shorter elimination half-life of midazolam is of greater significance if repeated doses are

given. The volume of distribution was increased in the elderly and in women.[16] It is increased greatly in obese patients because of the enhanced distribution of midazolam into peripheral adipose tissue with prolongation of the elimination half-life.[16]

The pharmacokinetics of midazolam are influenced by age. In one study involving a series of elderly as opposed to young male volunteers, the elimination half-life of midazolam was prolonged more than twofold, with total metabolic clearance reduced accordingly.[16] Furthermore, a long elimination half-life for midazolam has also been reported in six per cent of healthy subjects, who had an elimination half-life of between 8 and 22 hours, rather than three hours which is more typical of a healthy population.[19]

Midazolam is five times more potent than diazepam[17] and "valium" "Roche" is 1.3 times more potent than Diazemuls.[18] From the above, one might calculate an equivalent dosage ratio of about 6.5:1 for Diazemuls: midazolam. However, in the present study, a dosage ratio of 4:1, Diazemuls:midazolam was used and this may explain the findings in the present study that midazolam had a greater sedative effect and a slower recovery than Diazemuls.

It has been shown that the injection of midazolam and diazepam intravenously in equipotent doses depresses respiration similarly and that these effects are due to a depression of the central respiratory drive.[20] Low sedative doses of midazolam 0.075 $mg \cdot kg^{-1}$ IV do not affect the ventilatory response to CO_2, suggesting that in low doses, clinically important respiratory depression does not occur.[21] In our study, one patient in the midazolam group and four from the Diazemuls group had episodes of apnoea as detected by mass spectrometry. Intravenous fentanyl received by both groups may have contributed to the apnoeic episodes. Although oxygen saturation was never significantly decreased at any point in the apnoeic period, this stresses the importance of and necessity for adequate monitoring in conscious, sedated patients.

Diazepam, when dissolved in propylene glycol, causes a high incidence of venous thrombosis. A major advantage of midazolam is its water solubility and its low reported incidence of venous irritation due to thrombophlebitis. In contrast, venous sequelae have also been reported to occur with similar frequency after intravenous administration of midazolam and Diazemuls.[15] However, in our study, a significantly larger number of patients complained of mild tenderness at injection sites when Diazemuls was administered.

In summary, we have shown that both midazolam and Diazemuls are effective for sedation in cataract surgery. In a dose ratio of 1:4, midazolam produces better sedation but a more prolonged recovery than Diazemuls in elderly patients. Anterograde amnesia was comparable in the two groups, while more patients in the Diazemuls group developed episodes of apnoea.

Acknowledgments

We thank Miss Christine Drane for secretarial assistance and Mr. Anthony Ayiomamitis for statistical assistance.

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