Evaluation of the Anxiolytic and Amnestic Effects of Diazepam and Midazolam for Minor Oral Surgery

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Summary

Thirty three healthy patients (ASA 1) who required the removal of impacted third molars were included in a double-blind cross-over trial to compare the amnestic and anxiolytic efficacy of diazepam and midazolam. The anxiolytic properties of the two drugs were assessed objectively by the measurement of changes in blood pressure, pulse rate, plasma cortisol levels, and subjectively by a patient assessment using a visual analogue scale for anxiety. The amnestic properties were evaluated by patient's ability to recall two visual stimuli they were shown. The first drug given was titrated to clinical sedation and the second drug was given in an "equipotent" ratio of 1.0 midazolam to 2.86 diazepam. There was a statistically significant fall in anxiety and good levels of amnesia achieved using both drugs. No statistical differences were detected between the two drugs.

Introduction

The benzodiazepine drugs have been used for many years as intravenous sedation agents. They are widely used in oral surgery for their anxiolytic and amnestic properties. The benzodiazepine most commonly used over the last 15 years is diazepam. An intralipid preparation of diazepam (Diazemuls, Kavibitrim Ltd., United Kingdom) reduces the irritant effects of the propylene glycol component of the vehicles used for injectable diazepam. Midazolam has recently been introduced and has several claimed advantages over diazepam, primarily that of faster onset and recovery as well as enhanced amnestic qualities. The pharmacology of these drugs is well documented.[1,2] The aim of this trial was to evaluate the amnestic and anxiolytic qualities of the two preparations.

Methods

Thirty-three patients who required the removal of similarly impacted lower third molars were included in the trial. The study had the approval of the institutional review board and each patient gave their informed written consent. All the lower third molars were assessed radiographically to determine the degree of impaction. This was measured by a six point scale evaluating the depth of the impaction and the amount of surrounding bone (Table 1).

Twenty-seven females and six males were included in the study; the mean age at surgery was 24.2 years (range 18–51 years). All patients were healthy (ASA 1) with no contraindications to the use of local anesthetic and sedation. Patients who had taken sedative agents within the past month were excluded. The drug order and the side to be operated on first were randomly allocated.

On arrival each patient was placed supine (waiting time was kept to a minimum), their blood pressure (BP) and pulse rate (PR) were measured manually. Each patient was asked to indicate on a measured 10 cm visual analogue scale (VAS) their level of anxiety at that time (Fig. 1). The visual analogue scale was a 10 cm long line with zero cm being "totally relaxed" and ten cm being the "worst fear imaginable." To maintain double-blind conditions, one investigator took all the measurements while a second investigator administered the drugs and undertook the operative procedure. The operator placed an intravenous cannula into a large vein in the patient's forearm and drew off 5 ml of blood for plasma cortisol measurement. The cannula was kept patent by inject-

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Table 1. Radiographic Scoring for Impacted Lower Third Molar Teeth

Depth of impaction to the point of application of an elevator		Amount of bone encasing the crown of the tooth
0–5 mm	1	No part embedded in bone
5–10 mm	2	Less than half embedded
10 mm	3	Greater than half embedded

Each lower third molar is scored on two points and the scores added together.

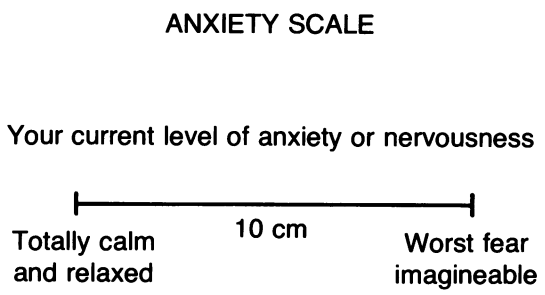

Fig. 1 — Anxiety Scale.

ing 2 ml of heparinized saline. The trial drug was then injected slowly over a time period of at least 2 minutes until the patient was judged by the operator to be clinically sedated. Markers used to access sedation included the presence of Verill's sign, slurred speech, drowsiness, and/or the patient stating that they felt relaxed. The end of administering the sedation agent was designated as time zero.

Two minutes later local anesthetic consisting of prilocaine 3% with felypressin 0.03 IU/ml. was administered (mean total dose 4.8 ml). Five minutes after time zero the patient was again asked to fill in a VAS, in a manner such that the patient could not see where they had placed their mark on the previous scale. The patient's BP and PR were again measured. They were then shown a picture of a brightly colored large animal on a white background at one meter for 15 seconds and asked to name it. Surgery was then commenced. At 15 minutes surgery was interrupted if it had not been completed. The patient was again asked to complete a VAS and his BP and PR were measured. The total time for surgery was recorded. At 30 minutes, 10 ml of venous blood was drawn off and discarded, and then a further 5 ml was taken for plasma cortisol measurement. The intravenous cannula was withdrawn and the patient's BP and PR measured. A different picture of another large animal was shown in the same manner as before. Finally, the patient was asked to fill in another VAS. The patients were kept at least half an hour before being discharged in the care of a responsible adult with the usual postoperative and postsedation instructions.

All patients were seen at one week to assess healing and were asked to recall the two animal pictures they were shown. After at least one further week (i.e., 2 weeks after the first operation), surgery on the second side was undertaken. The same procedure was followed except the second trial drug was used and different animal pictures were shown (a total of 4 were used). The trial drugs were administered in an "equipotent" ratio of 1 midazolam to 2.86 diazepam. This ratio was established by a retrospective analysis of 40 patients who had attended the oral surgery clinic for the removal of their impacted third molar teeth. The patients were treated by one surgeon using the same criteria for sedation as outlined above. Twenty patients had been given Diazemuls and 20 received midazolam. Both groups contained similar populations. The mean dosage of diazepam used was 15.11 mg and that of midazolam 5.29 mg, hence a relative potency ratio of 1 midazolam to 2.86 of diazepam was established. At the second appointment, the drug was not titrated but an "equipotent" amount of the second drug was given over the same time span as the first drug. The patients were reviewed at one week when they were asked to recall the animal pictures and also which drug they preferred.

The results were subjected to statistical analyses. The demographic data are presented in the usual fashion. The paired data, the radiographic scores for the left and right sides and the plasma cortisol levels, were subjected to a paired *t* test. All the repeated measurements, the VAS, BP, and PR, were compared using a repeated measure analysis of variance and a Newman-Keuls test. The McNemar test was used to statistically assess the difference between the two drugs with respect to the number of patients with recall for the pictures they were shown at the two time intervals. Drug preference by the patients was statistically compared using the Chi-square one-sample test.

Results

Both drug groups were similar for sex distribution, duration of surgery, and degree of impaction (Table 2). A mean dose of 4.7 mg of midazolam (range 3.5–7.0) was administered in comparison to 13.5 mg of diazepam (10–20).

TABLE 2. Group Composition with Regard to the Numbers and Sex of Patients, Duration of Surgery, Degree of Impaction, and Dose Administered

	Midazolam first	Diazepam first
No. of males	2	4
No. of females	16	11
Total	18	15
Average duration of surgery (min)	9.9	10.9
Degree of impaction	3.2	3.4

Patient assessment using VAS demonstrates a statistically significant fall in anxiety level following the administration of both sedative agents (Table 3) which was sustained throughout the procedure. Following the completion of the surgery, there was a further statistically significant fall in anxiety as demonstrated in the 30 minute VAS score. There were no statistically significant differences in anxiety levels measured by the VAS between the two drugs at any of the time intervals.

Systolic blood pressure decreased significantly ($p<0.05$) from presedation levels for both groups (Table 4) which was also sustained throughout the procedure. There was a slight, but significant increase in diastolic pressure from presedation levels ($p<0.05$) which was sustained throughout the procedure. PR decreased significantly from the presedation level by the 30 minute recording in both groups. There was no difference in PR between the two groups.

Serum cortisol levels decreased significantly ($p<0.001$) from presedation (537±268 nmol/L) to 30 minutes postmidazolam (444±241). A similar decrease from presedation (483±205) to postdiazepam (414±205) was also observed ($p<0.001$).

The number and percentage of patients with recall of the four pictures they were shown is documented in Table 5. Both drugs demonstrated a statistically significant ($p<0.05$) greater degree of amnesia at 5 minutes following the administration of the sedative agent than at 30 minutes. Patients showed no preference for either of the two drugs, they did however show a significant preference for the first procedure (Table 6).

Discussion

This study compared two benzodiazepines, midazolam and diazepam, in terms of their amnestic and anxiolytic qualities and patient preference for the drugs. A major problem in cross-over sedation

TABLE 3. Mean Anxiety Levels, as Measured by a Visual Analogue, of the Midazolam and Diazepam Groups at Each Time Interval

Mean anxiety ±standard deviation (mm measure of the horizontal VAS)	Time			
	Presedation	5	15 (min after sedation)	30
Diazepam	48±21[a]	26±13	34±22	21±18[c]
Midazolam	48±21[a]	30±17	32±20	21±20[b]

All values are statistically significant at the 5% level.
[a]Preop interval different from 5, 15, and 30 min.
[b]30 min interval different from preop, 5, 15 min.
[c]30 min interval different preop and 15 min.

Table 4. Mean Recorded Blood Pressure and Pulse Rate Effects for Diazepam and the Midazolam Groups at Each Time Interval

Mean pressures (mmHg)	Time			
	Presedation	5	15 (min after sedation	30
Midazolam				
(systolic)	117±17[a]	108±13	109±13	109±14
(diastolic)	77±9[b]	78±8	81±10	81±10
Diazepam				
(systolic)	115±16[a]	109±16	111±17	109±16
(diastolic)	77±10[a]	81±12	83±13	82±13
Mean pulse rates (beats per min)				
Midazolam	74±9	71±8	72±8	70±6[d]
Diazepam	74±9	74±8	73±8	7p±8[c]

[a]Preop interval different from the other three time intervals.
[b]Preop interval different from the 15 min time interval.
[c]30 min time interval different from the preop time interval.
[d]30 min time interval different from the other three time intervals.

Table 5. Number of Patients with Recall for the Pictures Shown at 5 and 30 Min Following Diazepam or Midazolam

	No. of patients with recall	
	5 min picture	30 min picture
Midazolam	14 (42.4%) [a]	23 (69.6%)
Diazepam	13 (39.3%) [a]	24 (72.7%)

[a] $p<0.05$.

TABLE 6. Patient Preference for the Drugs Given and Order of Surgery (Number of Patients Out of Sample)

	Patient preference for sedative drug		Patient preference for order of surgery
Midazolam	15	First operation	22[a]
Diazepam	16	Second operation	9

[a] $p<0.05$.

studies is the difficulty of obtaining equal levels of sedation. The simple use of dose per kilogram, while clearly a standard regime, does not conform to the clinical use of any sedation technique. The benefit of intravenous sedation is that it can be titrated against the patient's response and not be given as a fixed dose. When titrating a sedating agent, however, objective measures for assessing the level of sedation are not easily established nor is it easy to reproduce the same level of sedation when conducting a cross-over study. By titrating the initial drug and then administering an equally potent amount of the second drug at the second visit some of these criticisms can be overcome, assuming that an equipotent ratio has been established between the two drugs. A retrospective analysis undertaken prior to the present study established an equipotent ratio of 1 midazolam to 2.86 diazepam. This falls within the range of previous studies which vary from 1:1.5 to 1:4 (midazolam to diazepam).[4-9] The mean dosage of benzodiazepines was 4.7 mg midazolam and 13.5 mg for diazepam. The potency ratio of midazolam to diazepam may be used by clinicians inexperienced with midazolam to establish a reasonable starting dose for titration. With these dosage levels no patient lost either consciousness or verbal contact throughout the procedure.

Previous studies have concentrated on the operator assessment of the quality of the sedation[5,7,8,10,11] and the anxiolytic effect, as opposed to the patient's assessment.[4,6,8,11,12] The authors, however, agree with Wickstrom *et al.* [13] when they state that the evaluation of sedative–hypnotic drugs should be undertaken both subjectively and objectively under double-blind and randomized conditions.

The objective assessment of anxiolysis should be made by a number of modalities to ensure reliability.[13] In this study changes in BP, PR, and serum cortisol levels were used. Care must be taken, however, with the use of changes in PR and BP in the assessment of anxiety, as Dionne *et al.* [14] showed that these variables may be independent of subjective assessment of anxiolytics in the conscious sedated patient. The cardiovascular effects of the benzodiazepines have been well documented.[8,10,15-19] All show a fall in the systolic BP following the administration of an intravenous benzodiazepine which is in agreement with the current study. PR appear to be more variable. Some authors[15,16] find slight falls in the PR immediately following the administration of midazolam. Others[19,20] report no significant change in the PR, whereas a third group[8,9,10,17] noted increased PR. The present study showed a fall in the PR at 30 minutes compared with the presedation levels with both drugs. However, the changes in PR are small and cannot be regarded as clinically significant. Overall, the cardiovascular response to both drugs appears to be slight and very similar.

Serum cortisol levels as well as BP and PR have been shown to rise significantly under the stress of oral surgical treatment.[21,22] The rise in serum cortisol levels demonstrated in nonsedated patients can be measured at thirty minutes.[21,22] Serum cortisol levels have been considered a useful objective parameter of anxiety and its use suggested in sedation trials.[23] Goldstein *et al.*[24] looked at serum cortisol levels among other things under the stress of third molar removal with and without intravenous diazepam and found no alteration in the levels. This may well have been due to the timing of the blood sampling which was at ten minutes and three hours postsedation. Recently Gram and Christensen[25] have confirmed that benzodiazepines cause a reduction in serum cortisol levels and postulate that this effect is mediated through gamma-aminobutyric acidergic receptors inhibiting the hypothalmic release of corticotropin releasing factor and that this may represent a mechanism of action for the anxiolytic effect of

benzodiazepines. In the present study serum cortisol levels dropped significantly after 30 minutes with both intravenous agents. A valid comparison between the two agents was not undertaken because surgeries were not scheduled for the same time of day and there is a well recognized normal diurnal fluctuation in serum cortisol levels. It is our conclusion that this study confirms the usefulness of serum cortisol levels as an objective biochemical indicator of anxiolysis in sedation trials.

A visual analogue scale has been found useful to measure subjectively a patient's anxiety level.[26] A significant fall in anxiety level following the administration of both agents is demonstrated in this study. The anxiolytic effect was sustained throughout the procedure although there was a slight rise in anxiety levels at the 15 minute measurement which did not reach presedation levels. This probably reflects a slight rise in anxiety during surgery which was interrupted when necessary to make the recording. On completion of the procedure there is again a fall in anxiety level which is reflected at the 30 minute recording. There was no differences between the agents. There was also no difference between the first and second operation which is at variance with the cross-over study of Lundgren.[30]Lundgren's study,[30] however, did not use intravenous agents.

The amnestic action of diazepam and midazolam is well recognized and is considered one of the principal advantages of benzodiazepine sedative agents.[28-31] The amnestic action of both diazepam and midazolam appears to be dose dependent, being greater at higher doses, and time dependent, being greatest at the time of maximum sedation.[28-31] The onset of amnesia appears to correlate with the onset of clinical sedation and there is no retrograde amnesia.[28,29,31] It has been suggested that there is no difference in recall between 24 hours and one week, therefore, in our study, we coincided the test of recall with the normal postoperative appointment.[28] Visual picture stimuli are believed to provide the best test of memory recall.[28] Cutaneous pain such as local analgesic injections are more easily forgotten.[28] Most comparative trials of diazepam and midazolam have implied that the amnestic properties of midazolam might be greater.[4-6,8,10,12] The present study found no difference between the two agents in the picture recall at 5 or 30 minutes.

There are several possible explanations for this. Firstly, most other studies have used lower diazepam:midazolam ratios than the present study.[5-7,12] Hence a greater dose of midazolam was used and since amnestic properties can be dose related, midazolam may appear to be more amnestic. Other studies[9] demonstrated no differences between the amnestic properties of the two drugs when a similar potency ratio was used. Secondly, care must be taken in the timing of recall events, since the speed of onset of the two drugs may differ, midazolam taking approximately 2 minutes and diazepam 3 minutes to reach clinical onset.[6,12] Therefore, if a test of amnesia is given too close to the end of administering the sedation, the full amnestic properties may not have been given a chance to work. This study confirms the difference in amnesia between 5 and 30 minutes.[5,9,31] Thirdly, lack of a true dose-response curve prevents qualitative comparisons in amnesia between these two drugs.

A cross-over study provides a good opportunity for patients to express a preference for one agent or the other. In this study the two drugs were nearly equally preferred. However, of particular interest was that the first drug, irrespective of the agent used, was preferred by 22 patients and the second by only 9. This is a well recognized phenomenon.[32] When patients were asked, in this study, why they preferred the first drug, most stated that they felt more sedated the first time. However, when the data was analyzed, comparing the first and second appointments, we were unable to demonstrate any differences in the levels of anxiety measured subjectively or objectively. This may be because at the time of inquiring about preference, the first appointment was more remote than the second surgery with its associated anxiety and postoperative discomfort.

In conclusion, this study confirms the excellent anxiolytic and amnestic qualities of both benzodiazepines. It has demonstrated the cardiovascular effects following the administration of both drugs, in the sedation setting, which must be considered in its clinical use, particularly in the elderly. It has confirmed the usefulness of the anxiety VAS, when it is combined with other modalities, in assessing changes in anxiety levels. The excellent amnestic properties of both drugs has been demonstrated and it was shown that there is still significant amnesia present at 30 minutes. Patients preferred both drugs equally but had a significant preference for the first drug they were given. No differences in the amnestic and anxiolytic properties of the two drugs could be demonstrated.

References

1. Greenblatt DJ, Shader RI, Abernethy DR: Current status of benzodiazepines. N Engl J Med 309:354-358, 1983.
2. Kanto JH: Midazolam: The first water-soluble benzodiazepine. Pharmacology, pharmacokinetics, and efficacy in insomnia and anesthesia. Pharmacotherapy 5:138-155, 1985.
3. Seymour RA, Meechan JG, Blair GS: An investigation into post-operative pain after third molar surgery under local analgesia. Br J Oral Maxillofac Surg 23:410-414, 1985.
4. Aun C, Flynn PJ, Richards J, Major E: A comparison of midazolam and diazepam for intravenous sedation in dentistry. Anaesthesia 39:589-593, 1984.
5. Barclay JK, Hunter KM, McMillan W: Midazolam and diazepam copared as sedatives for outpatient surgery under local analgesia. Oral Surg 59:349-355, 1985.
6. Whitwam JG, Al-Khudhairi D, McCloy RF: A comparison of midazolam and diazepam in doses of comparable potency during gastroscopy. Br J Anaesth 55:773-777, 1983.
7. McGimpsey JG, Kawar P, Gamble JAS, Browne ES, Dundee JW: Midazolam in dentistry. Br Dent J 155:47-50, 1983.
8. Berggren L, Eriksson I, Mollenholt P, Wickban G: Sedation for

fibreoptic gastroscopy: A comparative study of midazolam and diazepam. Br J Anaesth 55:289-296, 1983.
9. Kortilla K, Tarkkamen J: Comparison of diazepam and midazolam for sedation during local anaesthesia for bronchoscopy. Br J Anaesth 57:581-586, 1985.
10. McClure JH, Brown DT, Wildsmith JAW: Comparison of the i.v. administration of midazolam and diazepam as sedation during spinal anaesthesia. Br J Anaesth 55:1089-1092, 1983.
11. Magri VC, Frost RA, Leung JWC, Cotton PB: A randomised comparison of midazolam and diazepam for sedation in upper gastrointestinal endoscopy. Br J Anaesth 55:1095-1100, 1983.
12. Al-Khudhairi D, Whitwam JG, McCloy RF: Midazolam and diazepam for gastroscopy. Anaesthesia 37:1002-1006, 1982.
13. Wickstrom E, Allgulander C: Comparison of quazepam, flunitrazepam and placebo as single dose hypnotics before surgery. Euro J Clin Pharmacol 24:67-70, 1983.
14. Dionne RA, Driscoll EJ, Butler DP, Wirdzek PR, Sweet JP: Evaluation by thoracic impedance cardiography of diazepam, placebo, and two drug combinations for intravenous sedation of dental outpatients. J Oral Maxillofac Surg 41:782-788, 1983.
15. Boralessa H, Sewar DF, Whitwam JG: Cardiovascular resonse to intubation. A comparative study of thiopentone and midazolam. Anaesthesia 38:623-627, 1983.
16. Lebowitz PW, Cote ME, Daniels AL, Ramsey FM, Martyn JAJ, Teplick RS, Davison JK: Comparative cardiovascular effects of midazolam and thiopental in healthy patients. Anesth Anal 61:771-775, 1982.
17. Reves JG, Samuelson PN, Lewis S: Midazolam maleate induction in patients with ischaemic heart disease. Haemodynamic observations. Canad Anaesth Soc J 26:402-409, 1979.
18. Kawar P, Carson IW, Clarke RSJ, Dundee JW, Lyons SM; Haemodynamic changes during induction of anaesthesia with midazolam and diazepam in patients undergoing coronary artery bypass surgery. Anaesthesia 40:767-770, 1985.
19. Brown CR, Sarnquist FH, Canup CA, Pedley TA: Clinical electoencephalographic and pharma cokinetic studies of a water soluble benzodiazepine, midazolam maleate. Anesthesiology 50:467-470, 1979.
20. Dixon J, Power SJ, Grundy EM, Lumley J, Morgan M: Sedation for local anaesthesia. Comparison of intravenous midazolam and diazepam. Anaesthesia 39:372-376, 1984.
21. Summers L: An investigation into the effects of surgical stress on the fit and poor risk patient including the modifying effects of relative analgesia and beta-blockage. Part 1 The effects of surgical stress on fit and poor risk patients. Br J Oral Surg 19:3-12, 1981.
22. Shannon IL, Isbell GM, Prigmore JR, Hester WR: Stress in dental patients. 2. The serum free 17-hydroxycorticosteroid response in routinely appointed patients undergoing simple exodontia. Oral Surg 15:1142-1146, 1962.
23. Norris W: The quantitative assessment of premedication. Br J Anaesth 41:778-784, 1969.
24. Goldstein DS, Dionne R, Sweet J, Gracely R, Brewer HB, Gregg R, Keiser HR: Circulatory, plasma catecholamine, cortisol, lipid, and psychological responses to a real-life stress (third molar extraction): Effects of diazepam sedation and of inclusion of epinephrine with the local anesthetic. Psychosom Med 44:259-272. 1982.
25. Gram LF, Christensen P: Benzodiazepine suppression of cortisol secretion: A measure of anxiolytic activity? Pharmacopsychiatrist 19:19-22, 1986.
26. Pinnock C, Fell D, Hunt P, Miller R, Smith G: A comparison of triazolam and diazepam as premedication agents for minor gynaecological surgery. Anaesthesia 40:324-328, 1985.
27. Gelfman SS, Gracely RH, Driscoll EJ, Wirdzek PR, Sweet JB, Butler DP: Conscious sedation with intravenous drugs: A study of amnesia. J Oral Surg 36:191-197, 1978.
28. Gregg JM, Ryan DE, Levin KH: The amnesic actions of diazepam. J Oral Surg 32:651-664, 1974.
29. Kortilla K. Linnoila M: Recovery and skill related to driving after intravenous sedation: Dose-response relationship with diazepam. Br J Anaesth 47:457-463, 1975.
30. Lundgren S: Comparison of rectal diazepam and subcutaneous morphine-scopolamine administration for outpatient sedation in minor oral surgery. Acta Anaesth Scan 29:674-678, 1985.
31. Dundee JW, Wilson DB: Amnesic action of midazolam. Anaesthesia 35:459-461, 1980.
32. Dixon RA, Kenyon C, Marsh DR, Thornton JA: Midazolam in conservative dentistry. A cross-over trial. Anaesthesia 41:276-281, 1986.