EVALUATION OF MIDAZOLAM AND DIAZEPAM FOR PRE-OPERATIVE SEDATION

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ABSTRACT

An open randomised, comparative study was planned to evaluate efficacy and tolerability of intramuscular midazolam and oral diazepam for preoperative sedation of patients under anaesthesia. 113 patients [diazepam=57;midazolam=56] of ASA grade I-II; between 18-60 years of age of either sex participated. Greater anxiety relief ($p < 0.0001$) was observed in the midazolam group compared to the diazepam group. Midazolam produced better clinically acceptable sedation of short duration. Excellent anterograde amnesia was seen with midazolam with lack of recall of intraoperative events during surgery. Cardiovascular stability was seen with both the drugs. Global quality of premedication assessed by the anaesthesiologist was excellent or good with midazolam as compared to satisfactory or poor with diazepam.

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KEY WORDS : Anaesthesia; Benzodiazepines-midazolam; Drugs; Premedication; Pre-operative sedation.

Introduction

The benzodiazepines exhibit anxiolytic, sedative, amnesic and anticonvulsant properties. They differ mainly in their pharmacokinetic properties, some being relatively short acting whereas others are only slowly eliminated. For many years diazepam has been the dominant sedative and anxiolytic for oral premedication. It is rapidly absorbed when given by mouth and in the standard dose of 10 to 20 mg exerts an anxiolytic action similar to that of morphine [1]. Diazepam causes anterograde amnesia and is devoid of emetic side effects. Its main disadvantages are a variable and unpredictable anxiolytic and sedative action and a long elimination half life. Its duration of action is further prolonged by active metabolites. Intramuscular injection is painful and is not recommended.

Midazolam is a water soluble benzodiazepine, a member of a new class of imidazobenzodiazepine derivative [2,3]. It is water soluble at pH < 4 but becomes highly lipid soluble at physiologic pH. Water solubility minimizes pain at the injection site. The lipid solubility ensures rapid distribution in tissues. Midazolam is more potent, has a faster onset and shorter duration of action than diazepam. The elimination half life is 1.5 to 3.5 hours as against approximately 20 hours [4] in case of diazepam. The metabolites of midazolam have negligible soporific effects. These properties make midazolam a suitable agent for producing conscious sedation in short endoscopic procedures, pre-operative sedation and for induction of general anaesthesia. Midazolam is formulated in an

injectable form for the above indications [2,3]. In clinical trials, midazolam has been found to provide pre-operative sedative effect superior to that of diazepam [5,6]. The drug has shown good local tolerability as well as good haemodynamic stability. The objective of the study was to evaluate the efficacy and tolerability of intramuscular midazolam and oral diazepam for pre-operative sedation of patients undergoing elective surgery under general anaesthesia. This was an open, randomised, comparative, study of 24 hours duration.

Inclusion Criteria

Patients fulfilling the following criteria were included in this study; patients of either sex aged between 18-60 years, ASA Class I (i.e. a healthy patient with no systemic disease) or patients in ASA Class II (i.e. a patient with a mild to moderate systemic disease caused either by the condition to be treated surgically or other pathological process which does not limit the patient's activities in anyway) e.g. mild diabetic, treated hypertensive or heavy smoker and posted for surgery under general anaesthesia with gas-oxygen-narcotic-relaxant technique.

Exclusion Criteria

Patients excluded were : pregnant or lactating females, patients with decompensated hepatic or renal disease, those unable or unwilling to give informed consent, hypersensitive to or had contraindications to the use of benzodiazepines or receiving benzodiazepines or any CNS depressant for any reason, history of alcohol, benzodiazepine or other drug abuse.

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Material and Methods

Patients were randomized to receive midazolam or diazepam. Midazolam was administered by deep intramuscular injection at a dose of 80 micrograms per kg body weight or a maximum of 5 mg one hour before surgery. Diazepam was administered orally at a dose of 10 mg (2 tablets) 1½ hours before surgery. Midazolam hydrochloride was supplied as 1 ml ampoules containing midazolam HCL 5 mg/ml (Batch No.AG-442-54) by Ranbaxy Laboratories Ltd. Diazepam was supplied as tablets of 5 mg. (Batch No.P00796). Medication was administered according to randomized schedule prepared by using PROC PLAN in SAS Software, Version 6.11.

Concomitant Therapy

Medication considered necessary for the patients welfare and which did not interfere with the study medication was allowed to be continued. The use of other benzodiazepines or any central nervous system depressants, which could interfere with the evaluation of efficacy, safety and tolerability was prohibited.

The efficacy variables in this study were :

- I. Anxiety assessed on Visual Analogue Scale.
- II. Level of sedation achieved.
- III. Anterograde amnesia.

The efficacy assessments were done immediately before drug administration and upto 1 hr. after drug administration in the case of midazolam and upto 1½ hours in the case of diazepam. However, assessment for recall (anterograde amnesia), was done 24 hours after preanaesthetic medication. Global evaluation of the quality of premedication was made 24 hours after premedication by the physician.

The safety variables were respiratory rate, heart rate and blood pressure before and after drug administration at various assessment points. Adverse experiences were recorded and classified as to their type, severity or casual relationship. Tenderness at the injection site was checked 24 hours after drug administration.

Written informed consent was obtained from patients posted for surgery under general anaesthesia, inclusion/exclusion criteria were applied and those fulfilling them were enrolled in the study. A complete medical history was obtained including demographic data, ASA functional class, concurrent illnesses and drug history. A physical examination was performed. Body weight was recorded.

A blood sample was obtained for estimation of haemoglobin, total leukocyte count, urea, serum creatinine, serum protein, albumin/globulin ratio, serum bilirubin, AST, ALT and serum alkaline phosphatase. Urine analysis was also performed, X-ray chest and ECG (if patient was more than 40 years old) was done.

Patients were brought to the preoperative area one and a half hours before the scheduled time of surgery. They were asked to score their anxiety level on a visual analogue scale. An intravenous line was established and vital signs (blood pressure, heart rate and respiratory rate) were recorded. The study medication was assigned to the patient as per the prepared randomization schedule. Midazolam was administered by deep intramuscular injection at a dose of 80 micrograms per kg body weight upto a maximum of 5 mg one hour before surgery; diazepam was administered orally at a dose of 10 mg (two tablets) one and a half hour before surgery. Vital signs were recorded 15 minutes, 30 minutes and 1 hours (for midazolam) and also at 1.5 hours (in case of diazepam) after sedation level was recorded by the investigator as not drowsy, moderately drowsy, asleep but responsive or asleep and non responsive.

The patient was asked to score his anxiety level against this time point on a Visual Analogue Scale. Also at this point, patient was shown a memory card with a picture of a one rupee note and asked to identify the picture verbally. The surgical procedure was to commence 1 hour after the administration of midazolam and 1.5 hours after administration of diazepam. On being wheeled into the operation theatre, patients were told that they were entering the theatre. They were also shown the operation theatre surgical light inside.

Twenty-four hours later, physicians were asked to rate the pre-medication as excellent, good, fair or poor (or unacceptable). Patients were asked if they remembered being taken into the operation theatre, being shown the surgical light, being shifted from the stretcher to the operating table and whether they recalled the memory card. If they did not, they were shown a composite card of 6 pictures in which the picture shown previously (i.e. the picture of a one rupee note) was included and the patients were asked to pick the picture shown to them previously. The injection site was examined for any tenderness. The anaesthesia notes and post-operative notes were examined for any anaesthetic or surgical adverse effects related to the drug

Statistical Analysis

Continuous efficacy variables were analysed using student 't' test. Categorical variables were tested using the Chi square test. The comparisons were two tailed and the level of alpha was set at 0.05. Analyses were performed on SAS software, version 6.11. Adverse experiences were reported.

Results

One hundred and thirteen patients participated in this study . The distribution of the patients in the two groups and their demographic characteristics is shown in Table 1. Six patients in this study had hypertension. They were under treatment with central sympathetic depressants, beta-blockers or calcium channel blockers. Two patients were receiving oral antidiabetic glibenclamide. Two patients who had bronchial asthma received bronchodilators. Eight persons received preoperative antibiotics.

Anxiolytic Effects

Anxiety score self assessed by patients on a visual analogue scale, before the administration of the preoperative sedatives and at various time points after the drug administration is shown in Table-2. Similarly mean anxiety score reductions from baseline in the diazepam and midazolam groups is shown in Table 3. Anxiety sedation from baseline at all time points for either drug was statistically significant ($p < 0.0001$). Greater anxiety relief was observed in the midazolam group compared to the diazepam group. The intergroup differences in anxiety relief was statistically significant at 15,30,60 and 90 minutes.

Sedation

The degree of sedation achieved with midazolam and diazepam at various time intervals after drug administration is presented in Table 4. Thirty minutes after drug administration, thirty six patients (63.1%) in diazepam group and 5 patients (8.9%) in the midazolam group were rated as being drowsy. Moderately drowsy were 14 (24.8%) in the diazepam group and 30 (53.5%) in the midazolam group. 2 patients (3.5%) with diazepam and 7 patients (12.5%) with midazolam were found very drowsy. 4 patients (7.0%) and 12 patients (21.4%) in the diazepam and midazolam groups were asleep, but responsive, 2 patients (3.5%) in midazolam group were asleep and non-responsive.

Sixty minutes after drug administration : The number of pa-

TABLE 1

Patient data : Baseline characteristics

	Midazolam	Diazepam	p
Age (Yrs.) Mean $\pm$ SD	35.4 $\pm$ 11.9	35.1 $\pm$ 11.6	NS
Minimum/Maximum	18:53	14:61	
Sex (No. of Pts.)	56	57	
Male	24	9	< 0.002
Female	32	48	NS
Weight (Kg)			
Mean $\pm$ SD	58.4 $\pm$ 16.9	52.6 $\pm$ 11.5	NS
ASA (No. of Pts.)			
I	51	48	NS
II	6	9	NS

TABLE 2

Anxiety score (mm) on visual analogue scale (mean $\pm$ SD) before and after drug administration

	Immediately before drug administration	Time in mins after drug administration			
		15	30	60	90
Midazolam (n=56)	60.4 $\pm$ 14.5	39.2 $\pm$ 15.9	24.8 $\pm$ 9.9	24.8 $\pm$ 9.9	14.0 $\pm$ 6.9
p Value (Within group)	-	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Diazepam (n=57)	48.5 $\pm$ 13.9	42.2 $\pm$ 17.8	31.2 $\pm$ 14.8	28.15 $\pm$ 12.3	27.01 $\pm$ 12.0
p Value (Within Group)	-	< 0.0001	< 0.0001	0.0001	< 0.0001
p Value (between the group)	NS	< 0.0001	< 0.0001	< 0.0001	< 0.0001

TABLE 3

Mean anxiety score reduction from baseline with diazepam and midazolam

Time in minutes	Diazepam (n=57)	Midazolam (n=56)
15	6.32* $\pm$ 10.46	21.43* $\pm$ 18.73
30	17.37* $\pm$ 12.86	35.89* $\pm$ 16.60
60	20.44* $\pm$ 12.15	35.89* $\pm$ 16.60
90	21.58* $\pm$ 12.07	36.00* $\pm$ 11.74

*P < 0.0001, highly significant in favour of midazolam.

tients who were not drowsy after one hour of drug administration were 12(21.0%) and 2(3.5%) in diazepam and midazolam groups respectively. 32 patients (56.1%) who were treated with diazepam and 26 patients (46.4%) in midazolam group were moderately drowsy. 10(16.0%) and 14(25.0%) patients were drowsy in the diazepam and midazolam treated groups. There were 3 patients (5.2%) and 14 patients (25.0%) treated with diazepam and midazolam who were found asleep but responsive.

Ninety minutes after drug administration, 11 patients in midazolam group were assessed for the degree of sedation as they were not yet wheeled into the operation theatre. 2(18.1%) of these patients were moderately drowsy, 7(63.6%) were very drowsy and

2(18.1%) were asleep but responsive. The corresponding figures for the diazepam group were 6(10.5%) not drowsy, 38(66.7%) moderately drowsy, 11 (19.6%) very drowsy and 2 patients (3.5%) were asleep but responsive.

Amnesia

In Table 5, the amnesia effects of the premedicants i.e. recall being wheeled into the operation theatre, being shifted from trolley to operation theatre, being shown the surgical lights, and being shown a picture on a memory card, are depicted. Greater number of patients had amnesia for the preoperative events after the drug administration in the midazolam group than in diazepam group; 7(12.28%) and 26(46.02%). Patients did not remember being wheeled into the operation theatre in the diazepam and midazolam groups respectively. 13(23.0%) patients and 41 (72.56%) patients in the diazepam and midazolam groups did not recall being shown the surgical lights. The number of patients who had no memory of being shifted from the trolley to the operation table were 8(14.16%) and 39(79.02%) with diazepam and midazolam respectively. 6(10.60%) diazepam treated and 41 (72.56%) midazolam administered patients did not remember having been shown a picture on a memory card. Out of these 6 diazepam treated patients who were then shown the picture within a composite memory card carrying other pictures, 3 of them were able to identify the picture. In the midazolam group only 4 out of 39 patients (who had no recall of the memory card) were able to identify the previously shown picture in the composite card.

Cardiovascular and respiratory changes

The values for the heart rate, systolic blood pressure and respiratory rate at baseline and various time intervals after administration of the premedicants are shown in Table 6. There was mean decrease of 0.5 $\pm$ 5.6, 1.3 $\pm$ 7.0 and 2.3 $\pm$ 8.9 pulse rate in diazepam group and 1.9 $\pm$ 5.6, 3.6 $\pm$ 7.4, 4.8 $\pm$ 6.6 in midazolam group. Similarly, the mean reduction in systolic blood pressure at 30 mins and 60 min was 2.7 $\pm$ 5.9 mm Hg and 3.8 $\pm$ 7.2 mm Hg in diazepam group, in comparison to, 3.9 $\pm$ 5.9 and 5.1 $\pm$ 6.2 mm Hg in midazolam treated patients. Decrease in diastolic blood pressure (mean mm Hg) was insignificant in both the groups. Mean reduction in respiratory rate at 30 mins; (0.6 cycles per min for diazepam; 0.9 cycles per min for midazolam) and at 60 min., (1.0 cycle per min for diazepam and 1.1 cycle per min for midazolam) was statistically significant between the groups.

Table 7 gives the overall opinion of the physician about the global quality of premedication. In the majority of the patients (83.0%) in the diazepam group, the quality of premedication was fair or poor. Contrary to the results in the diazepam group, majority of the patients (89.4%) who were administered midazolam achieved excellent or good premedication.

Discussion

Previous studies in Western literature have shown that intramuscular midazolam is a good presurgical medicant, superior to diazepam. The present study was undertaken to assess the suitability of midazolam for preoperative medication in Indian subjects. Since diazepam, the prototype benzodiazepine, administered intramuscularly is erratically absorbed and has poor local tolerability at the site of injection, oral diazepam is widely used by many anaesthesiologists in India for preoperative medication. It was therefore considered appropriate to study intramuscular midazolam in com-

TABLE 4

Assessment of sedation number (%) patients at various time intervals after the administration of the drug

	Time in minutes					
	30		60		90	
	Midazolam (n=56)	Diazepam (n=57)	Midazolam (n=56)	Diazepam (n=57)	Midazolam (n=56)	Diazepam (n=57)
No drowsy (Level 1 sedation)	5 (8.9%)	36 (63.1%)	2 (3.5%)	12 (21.0%)	0 (10.5%)	6 (10.5%)
Moderately drowsy (Level 2 sedation)	30 (53.5%)	14 (24.8%)	26 (46.4%)	32 (56.1%)	2 (18.1%)	38 (66.7%)
Very drowsy (Level 3 sedation)	7 (12.5%)	2 (3.5%)	14 (25.0%)	10 (16.0%)	7 (63.6%)	11 (19.6%)
Asleep but responsive (Level 4 sedation)	12 (21.4%)	4 (7.0%)	14 (25.0%)	3 (5.2%)	2 (18.1%)	2 (3.5%)
Asleep but not responsive (Level 5 sedation)	2 (3.5%)	0	0	0	0	0
p Value (inter group) (Chi ²)	< 0.001 Highly Significant		< 0.001 Highly Significant		< 0.01 Highly Significant	

TABLE 5

Amnesia : Number (%) of patients

Preoper event	Drug administered				(Chi ²)
	Midazolam (n=56)		Diazepam (n=57)		
	Yes	No	Yes	No	
Being taken into the operation theatre	30 (53.07%)	26 (46.02%)	50 (88.24%)	7 (12.28%)	0.001
Being shown operation theatre surgical light	15 (26.54%)	41 (72.5%)	44 (77.80%)	13 (23.0%)	0.001
Being shifted from stretcher trolley to the operation table	17 (30.08%)	39 (79.02%)	49 (86.70%)	8 (14.16%)	0.001
Being shown a memory card with a picture	15 (26.54%)	41 (72.56%)	51 (90.26%)	6 (10.60%)	0.001
Does patient remember picture after being shown the composite memory card	(n=39) 4 (17.75%)	35 (82.3%)	(n=6) 3 (13.3%)	3 (13.3%)	

parison with oral diazepam for premedication.

The results of the present study show that intramuscular midazolam administered at the recommended dose of 80 microgram/kg body weight is a suitable premedicant for Indian patients in ASA Class I or II.

The present study has shown clearly that significantly better anxiolytic, sedative and anterograde amnesic effects are achieved with midazolam than with oral diazepam 10 mg, the dose at which diazepam is commonly used for premedication. This is in agreement with previous studies demonstrating a superior relief of preoperative anxiety with midazolam compared to diazepam [7]. Owing to the intramuscular route of administration, the effects of midazolam came on rapidly and generally within 15 minutes after administration. Diazepam in contrast had a delayed on-

set of action of about 30 minutes after administration. Adequate anxiolytic and sedative effects were found to persist upto 90 minutes after the administration of midazolam.

From the results of the present study it can be stated that intramuscular midazolam reliably and rapidly produces an appropriate degree of sedation and a better quality of sedation than diazepam in patients awaiting surgery.

The superior amnesic effects of midazolam compared to diazepam have been previously reported [7]. Diminished recall of events associated with surgical procedure is a highly desirable property of drugs used for preoperative medication in addition to anxiolysis and sedation. All these effects were produced reliably and to a greater degree with midazolam in this study.

TABLE 6
Changes in heart rate, blood pressure and respiratory rate (Mean $\pm$ SD)

	Midazolam (n=56)	Diazepam (n=57)	p Value
Heart rate			
Before drug administration	80.9 $\pm$ 9.2	83.5 $\pm$ 8.1	NS**
15 min after drug administration	79.00 $\pm$ 8.9	84.1 $\pm$ 7.7	NS*
30 min after drug administration	77.3 $\pm$ 7.6	82.2 $\pm$ 8.4	NS*
60 min after drug administration	76.1 $\pm$ 7.4	81.1 $\pm$ 9.0	NS*
Systolic blood pressure			
Before drug administration	124.4 $\pm$ 10.7	122.8 $\pm$ 12.3	NS**
15 min after drug administration	120.4 $\pm$ 11.3	122.2 $\pm$ 11.9	NS*
30 min after drug administration	120.5 $\pm$ 9.4	120.1 $\pm$ 11.5	NS*
60 min after drug administration	119.2 $\pm$ 8.9	118.8 $\pm$ 10.7	NS*
Diastolic blood pressure			
Before drug administration	81.4 $\pm$ 8.6	78.4 $\pm$ 8.2	NS**
15 min after drug administration	78.8 $\pm$ 8.5	77.7 $\pm$ 7.7	NS*
30 min after drug administration	77.8 $\pm$ 8.1	77.0 $\pm$ 7.1	NS*
60 min after drug administration	76.3 $\pm$ 8.4	76.8 $\pm$ 7.5	NS*
Respiratory rate			
Before drug administration	17.6 $\pm$ 1.0	18.4 $\pm$ 1.3	0.005
15 min after drug administration	17.0 $\pm$ 1.1	18.1 $\pm$ 1.25	0.001
30 min after drug administration	16.6 $\pm$ 1.0	17.7 $\pm$ 1.6	
60 min after drug administration	16.3 $\pm$ 0.7	17.4 $\pm$ 1.6	NS*

* - Comparison within groups of the mean change from baseline (two sample 't' test).

** - Comparison between groups of the mean values at the baseline.

TABLE 7
Global evaluation of premedication number (%) of patients

	Midazolam (n=56)	Diazepam (n=57)	p value Chi ²
Excellent	37 (66.4%)	2 (3.5%)	
Good	13 (23.0%)	8 (15.6%)	0.001
Fair *	6 (10.6%)	41 (72.4%)	
Poor (unacceptable)	0	6 (10.6%)	

From previous experience with midazolam, it is known that relatively small doses such as the dose used for presurgical medication do not compromise respiratory function. The results of the present study in which the respiratory rate was reduced by 7.5% in midazolam treated patients (published data-11% reduction in respiratory rate) are in confirmation of this fact [8].

Small reduction in blood pressure, and heart rate are expected effects of midazolam [8] and were seen in the present study as well. None of the patients in the present study had hypotension requiring treatment.

The local tolerability of midazolam injection in this study was better than in a published study in which a 4.0% incidence of pain/tenderness/erythema at the injection site was reported [8]. But it is in line with the total absence of any local side effect reported in another study with intramuscular midazolam [9]. Midazolam was well tolerated. Heart rate was essentially unchanged, and there was reduction in blood pressure both with diazepam and midazolam which was however not of a magnitude causing clinical concern; the reduction could also be a reflection of the anxiolytic effect of the drugs. Local tolerability of midazolam was excellent, there being no erythema, pain or tenderness at the injection site 24 hours after injection.

Midazolam hydrochloride administered intramuscularly at a dose of 80 microgram/kg body weight is a suitable premedicant in Indian patients of ASA Class I and II. Midazolam produced superior anxiolytic, sedative and anterograde amnesic effect compared to orally administered diazepam 10 mg. The systemic and local tolerability of intramuscular midazolam was good. Because of these clinical advantages, midazolam would be a very useful addition to drugs available for achieving preoperative sedation.

References

1. Haslet WHK and Dundee JW. Studies of drugs given before anaesthesia XIV : Two benzodiazepine derivatives chlor-diazepoxide and diazepam. *Br J Anaesthesia* 1968;40:250-8.
2. Dundee JW, Halliday NJ, Harper KW. Midazolam-A review of its pharmacological properties and therapeutic use. *Drugs* 1984;28:519-43.
3. Reves JG, Fragan RJ, Vinik HR. Midazolam: Pharmacology and uses. *Anesthesiology* 1985;62:310-24.
4. Kaplan SA, Jack ML, Alexander K. Pharmacokinetic profile of diazepam in man following single intravenous and oral and chronic oral administration. *J. Pharmacol. Sci.* 1973;62:1789-92.
5. Chasapakis G, Karatsaloar I, Partsalidon A. Midazolam (R O -21-3981) versus diazepam in premedication. *Acta Anaesthesia Helv* 1981;15:68-72.

6. Mattila MAK, Surinkovoinen S, Saila K. Midazolam and fat emulsion diazepam as intramuscular premedication - A double blind clinical trial. *Acta Anaesth Scand* 1983;27:345-8.
 7. Jullien Y, Holzer J, Passeran D. A comparison of midazolam and diazepam for intramuscular premedication *Ann.Fr.Anaesth.Reanim.* 1982; 1:23-7.
 8. Monograph-Midazolam hydrochloride. American Hospital Formulary Service. 1995; 28.24.08.
 9. Fragen RJ, Funk DI, Avram MJ. Midazolam vs Hydroxyzine as intramuscular premedicants. *Anaesthesiology* 1985; 55 (3): 278-81.
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