MIDAZOLAM, A NEW MORE POTENT BENZODIAZEPINE, COMPARED WITH DIAZEPAM AS SEDATIVE DURING SPINAL ANALGESIA, A RANDOMISED DOUBLE BLIND STUDY

Col YUDHVIR SURI, ^{vsm}*, Lt Col NS LAMBA ⁺

ABSTRACT

Midazolam, a new benzodiazepine was compared with diazepam as intraoperative sedative during spinal anaesthesia in a double blind study. Eighty five patients participated in this clinical trial (placebo 25, midazolam 30, diazepam 30). Drug treatment was administered after spinal anaesthesia at 5 min of supine position. Level of spinal anaesthesia in terms of sympathetic blockade was similar in all the patients. Dosage of drug were tailored to the needs of each patient till the end point of undisturbed sleep. Intraoperative sedation based on predetermined criteria, recovery by Trieger's test at 4 hr after the drug administration, antegrade amnesia by memory card and haemodynamics were assessed. Mean doses of 240 $\mu\text{g kg}^{-1}$ and 500 $\mu\text{g kg}^{-1}$ of midazolam and diazepam were required to induce sleep which suggest an equivalent dose ratio of midazolam: diazepam as 1: 2.1. Both the drugs produced effective sedation during spinal anaesthesia, 86.6% patient with midazolam and 93.3% patients with diazepam had deep undisturbed sleep. Clinical recovery was fast in midazolam administered patients but did not meet the criteria of early discharge by Trieger's test at 4 hr after the administration of the drug. There were no gross changes in the circulatory effects of the two drugs. Decrease in mean systolic pressure (<10%) and marginal increase in heart rate was seen. The frequency of antegrade amnesia was greater with midazolam. Global assessment as judged by anaesthesiologist and patients satisfaction for anaesthesia and recovery was higher (93.3%) with midazolam as compared to (79.9%) diazepam.

MJAFI 2000; 56 : 29-32

KEY WORDS: Benzodiazepine drugs; Intraoperative sedation; Midazolam; Spinal anaesthesia.

Introduction

Majority of the patients desire to sleep during regional anaesthesia. Diazepam has been widely used for this purpose. Midazolam is a imidazobenzodiazepine derivative, water soluble at pH<4 which has recently been introduced in India. It is short acting, more potent, metabolic elimination more rapid than that of diazepam and intravenous administration is neither painful nor-irritating [1]. This study was designed to assess the effectiveness and safety of midazolam compared with diazepam as sedative in patients during spinal analgesia.

Material and Methods

Eighty-five patients undergoing surgery to the lower abdomen, perineum or legs under spinal anaesthesia participated with informed consent. Permission from institutional ethics committee and Drug Controller of India was obtained to conduct this trial. Patients were allocated randomly to receive one of the drug treatment (Table 1) as sedation during the procedure. Drug treatments administered to the patients were coded. The study was blind to investigators assessing the patients. Recovery from drug treatment was assessed by (i) ability to obey command (ii) orientation in time, place and person (iii) recall of the procedure and (iv) Trieger's test [2] at 4 hr after the drug administration in the recovery room area of the operation theatre. Baseline Trieger test was performed on the day of surgery before administration of premedicant

drugs. Trieger test consists of a series of dots arranged in a simple pattern which the patient connects as accurately as possible. The accuracy and timings were compared with the baseline test carried out before premedication. Decrease in accuracy was measured by recording the number of dots missed and the cumulative distance of miss in mm, compared with the baseline test. Position of the patient, moderator staff, place, material and light were the same during performance of the test.

TABLE 1

Coding of drug treatment, grouping and number of patients

Grouping/Coding	Drug Treatment	Number of patients
Group 1 (Code 1)	Placebo	25
Group 2 (Code 2)	Midazolam	30
Group 3 (Code 3)	Placebo	30

Patients were premedicated with injection atropine 0.6 mg and injection fortwin 0.5 mg kg^{-1} intramuscularly one hour prior to surgery in the anaesthetic room and iv cannula was placed on the dorsum of the hand; heart rate, arterial pressure, level of sedation were recorded.

Lumbar puncture was performed in the sitting position at the 3rd interspace and 0.5% plain bupivacaine 4 ml was injected at 1 ml. 5 Sec⁻¹. The patients were returned to the supine position, heart rate, blood pressure and upper level of block (pinprick test of analgesia) were recorded every 5 min until spread ceased. Respiratory rate was also recorded. Drug (Placebo, midazolam and diaze-

* Senior Adviser (Anaesthesiology), Base Hospital, Delhi Cantt, 110 010 ⁺ Classified Specialist (Anaesthesiology), 428 Field Ambulance, C/o 56 APO.

pam) treatment was administered after spinal anaesthesia 5 min of supine position. The concentration of the midazolam and diazepam were 5 mg. ml⁻¹. The nature of the drug was not known to the investigators. The drug was administered at 1 ml min⁻¹ via the indwelling cannula which was not used for any other purpose. Drug dosage was tailored to the needs of each patient with small increments but with an interval of 1 min between the administration of drug supplements, until the end point of sleep, undisturbed by speaking or arterial pressure measurement was achieved. Airway obstruction, haemodynamics and respiratory rate were recorded at 10 min interval during anaesthesia. Patients were assessed by the predetermined criteria of level and quality of sedation: +4=asleep but not responsive, +3=asleep but responsive, +2=very drowsy, +1=moderately drowsy; 0=not drowsy at 10,30, 60

TABLE 2
Demographic data and ethnic population (n=85)

	Group 1	Group 2	Group 3
Age (yrs)	40.83	44.57	39.66
(Mean $\pm$ SD)	$\pm$ 08.21	$\pm$ 11.85	$\pm$ 09.55
Weight (Kg)	55.33	60.35	58.73
(Mean $\pm$ SD)	$\pm$ 12.50	$\pm$ 09.66	$\pm$ 12.53
Male	16	24	22
Female	9	6	8
North Indians	18	16	19
South Indians	7	14	11
Level of blockade	T 10 $\pm$ 0.5	T 10 $\pm$ 0.65	T 10 $\pm$ 0.7

North Indians: States of Punjab, Haryana, Uttar Pradesh, Himachal Pradesh, Union Territory of Chandigarh.

South Indians : States of Kerala, Assam, West Bengal, Andhra Pradesh and Tamil Nadu.

TABLE 3
Surgical procedure (number %) and duration of surgery (min)

Surgery	Group 1	Group 2	Group 3
Orthopaedics	20 (80.0)	25 (83.0)	23 (76.60)
General Surgery	2 (8.0)	2 (6.60)	3 (10.30)
Gynaec and Obstetrics	3 (12.0)	3 (10.0)	4 (13.30)
Duration of Surgery (mins)	112.25 $\pm$ 18.00	124.80 $\pm$ 15.30	122.51 $\pm$ 12.65

TABLE 4
Level of sedation : number of patients (%)

Level of sedation	Basal			Time in mins after drug treatment											
				10			30			60			≥60		
	1	2	3/4	1	2	3/4	1	2	3/4	1	2	3/4	1	2	3/4
Group I (n=25)	2 (8.0)	0	0	2 (8.0)	0	0	2 (8.0)	0	0	0	0	0	0	0	0
Group II (n=30)	1 (3.30)	2 (6.60)	0	4 (13.30)	6 (20.0)	20 (66.6)	4 (13.30)	8 (26.6)	18 (60.0)	8 (26.6)	10 (33.3)	12 (40.0)	24 (80.0)	1 (3.3)	0
Group III (n=30)	3 (9.90)	1 (3.30)	0	2 (6.66)	6 (20.0)	22 (73.3)	6 (20.0)	4 (13.3)	20 (66.6)	4 (13.3)	8 (26.6)	18 (60.0)	6 (20.0)	16 (53.3)	8 (26.6)

Level of sedation 0 = not drowsy; 1 = Moderately drowsy; 2 = very drowsy; 3 = Asleep but responsive; 4 = Asleep but not responsive.

and >60 min during surgery. Again, at the end of surgery, level, of consciousness was observed. Recall test of events and recovery by Trieger's test was performed. Global assessment was made based on patient's adaptability and anaesthesiologist's satisfaction of anaesthesia and recovery.

Results

Characteristics of the patients, ethnic population and blockade of dermatome level are shown in Table 2. Mean doses of midazolam 16.0 mg (240 μ g Kg⁻¹) and diazepam 30 mg (50 μ g kg⁻¹) were required to induce sleep. 26 (86.6%) patients in midazolam group and 28 (93.3%) patients in diazepam were judged to be in sleep whereas sedation was considered acceptable in other patients. Surgical procedures (Table-3) were mainly orthopaedic and the duration of surgery lasted between 45 min to 230 min. 6 (20.0%) patients who received midazolam woke up during surgery but remained calm and quiet. None required additional sedation after the initial sleep dose of the drug. At the end of the surgery, 4 h after the administration of the last dose of the drugs, 24 (80.%) patients were wide awake, calm-quiet; 5(16.6%) moderately drowsy and one (3.3%) was very drowsy but arousable with midazolam. In the diazepam group, 6(20.0%) were wide awake ; 16 (53.3%) moderately drowsy and 8 (26.6%) patients were still asleep but arousable. Subsequently, more patients were awake sooner in the midazolam group (Table 4). Trieger's test expressed as the change from the baseline (Table 5) showed clinically insignificant but statistically significant changes at 4 h after sedation.

There were small decreases in mean systolic arterial pressure and small increases in mean heart rate after both administration of the spinal anaesthesia and either sedative drug (Tables 6,7). Level of spinal anaesthesia in terms of sympathetic blockade was same in all the patients prior to drug treatment. Respiratory rate increased from 17.5 $\pm$ 1.56 bpm to 19.60 $\pm$ 1.35 bpm after midazolam and increased from 15.20 $\pm$ 1.25 bpm to 18.20 $\pm$ 1.50bpm after diazepam. These difference were not significant (P>0.5). The frequency of antegrade amnesia, as judged by memory card, was greater with midazolam. Incidence of global assessment (Table-8) as judged by anaesthesiologist and patient satisfaction for anaesthesia and recovery was higher 93.30% with midazolam as compared to 79.9% in diazepam.

Discussion

Midazolam, 70 μ g kg⁻¹ has been found to be equipotent to 150 μ g kg⁻¹ diazepam as conscious sedative [3]. Our aim was to induce undisturbed sleep in patients whose cooperation was not essential during surgery. We used dosage of drugs tailored to the needs

TABLE 5

Recovery : Trieger test performance. (Values mean $\pm$ SD)

Medication	Placebo	Midazolam	Diazepam	p
Number of dots missed				
Before medication	2.30 $\pm$ 0.55	4.80 $\pm$ 1.25	3.50 $\pm$ 1.82	ns
After premedication	4.81 $\pm$ 1.70	6.65 $\pm$ 2.60	5.90 $\pm$ 2.98	ns
4h after drug	3.69 $\pm$ 0.95	10.70* $\pm$ 4.85	12.55* $\pm$ 5.87	p < 0.05
Total length of miss (mm)				
Before medication	3.80 $\pm$ 2.15	5.59 $\pm$ 1.90	8.35 $\pm$ 5.30	ns
After premedication	5.95 $\pm$ 2.60	4.50 $\pm$ 2.11	10.32 $\pm$ 6.21	ns
4h after drugs	4.66 $\pm$ 2.80	9.56* $\pm$ 3.50	18.20* $\pm$ 5.10	p < 0.05
Time taken (sec)				
Before medication	15.50 $\pm$ 8.22	10.45 $\pm$ 8.30	7.18 $\pm$ 5.00	ns
After Premedication	17.00 $\pm$ 6.59	11.05 $\pm$ 7.90	12.56* $\pm$ 8.74	p < 0.05
4h after drugs	16.25 $\pm$ 9.25	15.70* $\pm$ 10.33	20.35* $\pm$ 12.05	p > 0.05

Significant (p < 0.05) relative to control premedication. P = mann-whitney test; ns = not significant.

of each patients till the end-point of undisturbed sleep. The equivalent dose ratio for midazolam: diazepam has been reported [4] as 1: 1.7-2 whereas our results suggest a ratio of 1:2.1. Premedication was considered essential, as a pilot study without premedication re-

TABLE 8

Global assessment : number (%)

	Group 1 (n=25)	Group 2 (n=30)	Group 3 (n=30)
Excellent	5 (20.0)	22 (73.30)	16 (55.30)
Good	12 (48.0)	6 (20.0)	8 (26.0)
Fair	8 (36.0)	2 (6.60)	6 (20.0)

sulted in an unacceptable frequency of vasovagal attacks following puncture.

Both the drugs produced effective sedation during spinal anaesthesia. More undisturbed patients were awake at 4h after the administration of midazolam than after diazepam. Recovery was similar in both the groups: Judged clinically, most patients had recovered, but their performance in Trieger testing significantly impaired at 4h after the administration of the drugs. This is consistent with published evidence for both the drugs [4,6]. Impaired cognitive response with diazepam and midazolam may be related to metabolites [7]. Three midazolam metabolites have been detected; 1-hydroxymethyl midazolam, 4-hydroxy midazolam which are pharmacologically active. Their potencies at equivalent molar concentrations appear to be substantially less than that of midazolam. Cresvoiseir and others [7] demonstrated that -hydroxymethyl midazolam

TABLE 6

Haemodynamic Changes : (Mean $\pm$ SD) systolic blood pressure

	Basal	Premedication		After Spinal analgesia	Time in Minutes after drug treatment			Post operative
		Before	After		10	20	30	
Group I	123.83 $\pm$ 16.20	118.51 $\pm$ 9.42	115.41 $\pm$ 15.05	108.22* $\pm$ 12.35	102.33* $\pm$ 14.55	90.16** $\pm$ 16.20	110.30 $\pm$ 12.72	116.00 $\pm$ 11.56
Group II	124.23 $\pm$ 12.53	121.71 $\pm$ 15.11	119.41 $\pm$ 12.69	111.64 $\pm$ 10.64	100.70* $\pm$ 14.35	96.82* $\pm$ 12.36	98.23 $\pm$ 13.59	111.64 $\pm$ 14.20
Group III	118.76 $\pm$ 11.35	116.20 $\pm$ 9.61	108.90 $\pm$ 12.70	102.53** $\pm$ 14.44	98.35** $\pm$ 12.59	90.20** $\pm$ 14.39	106.45 $\pm$ 12.55	110.29 $\pm$ 10.83

*p < 0.05, Significant; **p < 0.01 highly significant; compared to based value of the group; Intergroup comparison p > 0.5, not significant.

TABLE 7

Haemodynamic Changes : Pules rate min⁻¹ (Mean $\pm$ SD)

	Basal	Premedication		After Spinal analgesia	Time in Minutes after drug treatment			Post operative
		Before	After		10	20	30	
Group I	87.33 $\pm$ 9.06	90.35 $\pm$ 11.72	88.60 $\pm$ 12.30	91.20 $\pm$ 16.22	92.60 $\pm$ 12.15	96.30 $\pm$ 14.95	82.11 $\pm$ 9.30	76.79 $\pm$ 11.61
Group II	85.29 $\pm$ 12.00	88.05 $\pm$ 9.66	76.64 $\pm$ 12.53	85.05 $\pm$ 15.62	88.00 $\pm$ 12.29	87.94 $\pm$ 9.33	85.17 $\pm$ 12.95	79.64 $\pm$ 12.30
Group III	89.54 $\pm$ 12.46	92.00 $\pm$ 14.55	82.72 $\pm$ 10.58	98.54 $\pm$ 13.69	90.35 $\pm$ 14.08	92.57 $\pm$ 12.84	98.69 $\pm$ 16.23	92.85 $\pm$ 12.81

(principal metabolite) contributes to the central nervous system effects of midazolam.

Spinal anaesthesia may decrease the mean systolic blood pressure, degree of decrease depends on the level of dermatome blockade. Midazolam [8] decreases systemic vascular resistance, cardiac output, stroke index and cardiac index.

Concomitant administration [8] of an opiate agonist as premedication may increase the risk of hypotension. There were no gross changes in the circulatory effects of the two drugs. There was slight gradual decrease (<10%) in mean systolic arterial pressure and increase in heart rate after spinal anaesthesia, and administration of diazepam and midazolam. Khudhairi [9] reported 12% and 5% decrease in arterial pressure with midazolam 300 $\mu\text{g Kg}^{-1}$ but these changes were less dominant than diazepam 500 $\mu\text{g Kg}^{-1}$ in patients undergoing aortocoronary bypass surgery. Amnesia helps the patients to accept the regional anaesthesia without fear with high degree of satisfaction. Midazolam antegrade amnesia is well documented [11] in conformity with our study. Neither diazepam nor midazolam caused loss of airway. One patient developed urticaria, rash and pruritus with midazolam. No adverse respiratory effects were seen. Oxygen saturation was maintained 98-100% with sedation by midazolam or diazepam. Incidence of global assessment was significantly higher ($P < 0.01$) with midazolam (93.3%) vs diazepam (79.9%). Present study confirms the safety of midazolam as sedative. Midazolam is better alternative to diazepam for sedation, cardiovascular stability, amnesia and recovery as intravenous sedative during spinal anaesthesia.

REFERENCES

1. Reves JG, Corssen G, Holcomb C. Comparison of two benzodiazepines for anaesthesia induction: Midazolam and diazepam. *Can Assoc Soc J* 1978;25:211-13.
2. Newman MG, Trieger N, Miller JC. Measuring recovery from anaesthesia-a simple test. *Anaesth Analg* 1969;48:136-40.
3. Whitman GJ, Khudhairi DA, McCloy RF. Comparison of midazolam and diazepam in doses of comparable potency during gastroscopy. *Brit J anaesth* 1983;55:773-7.
4. Magni CV, Frost AR, Leung CWJ, Cotton BP. A randomised comparison of midazolam and diazepam for sedation in upper gastrointestinal endoscopy. *Brit J Anaesth* 1983; 55:1095-100.
5. Kavar P, McGimpsey JG, Gamble JAS, Browne ES, Dundee JW. Midazolam as a sedative in dentistry. *Brit J Anaesth* 1982;55:1137-9.
6. Baird ES, Hailey DM. Delayed recovery from a sedative: Correlation of the plasma levels of diazepam with clinical effects after oral and intravenous administration. *Brit J Anaesth* 1972;44:803-7.
7. Crevoiser C, Ziegler WH, Eckert M, Heizmann P. Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. *Brit J Clin Pharmacol* 1983;16:51 S.
8. Midazolam Hydrochloride, AHFS drug information 95, 28:24:08, 1597-1602.
9. Khudhairi DA, Whitwam GJ, Chakrabarti KM, Ashitopoulou H, Grundy ME, Powrie S. Haemodynamic effects of midazolam and thiopentone during induction of anaesthesia for coronary artery surgery. *Brit J Anaesth* 1982;54:881-4.
10. Kavar P, Carson IW, Lyons SM, Clarke RSJ, Dundee JW. Haemodynamic changes during induction of anaesthesia with midazolam and diazepam in patients undergoing aorto-coronary bypass surgery. *Brit J Anaesth* 1983;55:915P.
11. Dundee JW, Halliday NJ, Harper KW, Brogden RN. Midazolam -A review of pharmacological properties and therapeutic use. *Drug* 1984;28:519-43.