Comparison of midazolam and diazepam to supplement total intravenous anaesthesia with ketamine for endoscopy

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Fifty patients undergoing endoscopy (laryngoscopy, bronchoscopy, mediastinoscopy) were anaesthetised in a double-blind prospective trial using total intravenous anaesthesia. Half of the patients were anaesthetised with an infusion of a solution of 250 mg ketamine and 12.5 mg midazolam. The other patients received an infusion of a solution of 250 mg ketamine and 20 mg diazepam. In addition, both groups were given increments of 50–100 μg of fentanyl. The immediate awakening time (t_1) was not significantly different between groups, but the patients who had received midazolam-ketamine, had a significantly shorter time to more complete recovery (t_2), a significantly lower frequency of emergence reactions and were more satisfied with the anaesthetic than the patients who had received diazepam-ketamine. There was no difference between groups with respect to intraoperative heart rate and blood pressure. No awareness during anaesthesia was reported.

The high frequency of emergence reactions in association with ketamine anaesthesia is well known.[1] By combining ketamine with a benzodiazepine the psychomimetic side effects and the cardiovascular stimulating effects of ketamine can be reduced significantly.[2–4] Ketamine has often been given in combination with diazepam. A problem associated with the use of diazepam is the long elimination half-life and its pharmacologically active metabolites.[5]

Midazolam is a newer water-soluble benzodiazepine with a shorter elimination half-life than diazepam and no pharmacologically active metabolites.[6] The comparable dose ratio between diazepam and midazolam is difficult to assess, as there is great individual variation, unrelated to weight, in response to benzodiazepines.[6] Equipotent doses of diazepam:midazolam have been estimated to be from 2:1 to 1.5:1.[6,7] Cartwright and Pingel[8] compared diazepam and midazolam (ratio 1.7:1) and found that midazolam was superior to diazepam in preventing unpleasant dreams in association with ketamine anaesthesia, although it did not offer any advantage in reducing emergence delirium.

We designed a double-blind prospective trial to compare midazolam with diazepam using total intravenous anaesthesia with ketamine-benzodiazepine-fentanyl. We chose to compare diazepam:midazolam in a ratio 1.6:1. We were interested in seeing whether midazolam was superior to diazepam in preventing emergence delirium as well as dreaming, and if it was associated with the same degree of cardiovascular stability. At the same time we wanted to determine whether the shorter elimination half-life of midazolam would result in a shorter awakening time, in association with ketamine anaesthesia.

Key words
ANAESTHESIA: total intravenous; HYPNOTICS, BENZODIAZEPINES: diazepam, midazolam; ANAESTHETICS, INTRAVENOUS: ketamine; RECOVERY.

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Methods

Fifty adult patients undergoing bronchoscopy, mediastinoscopy or laryngoscopy, or combinations of these procedures, participated in the study. Patients with a history of arterial hypertension, ischaemic heart disease or mental illness were excluded. Patients were allocated in a random and double-blind fashion two groups of 25 patients each. The patient, the anaesthetist and the observer were all blinded. The study protocol was approved by the local ethics committee, and the patients gave their consent.

All the patients were premedicated with intramuscular morphine 7.5 mg and scopolamine 0.3 mg half an hour before the start of anaesthesia. Scopolamine was given to reduce the salivary secretions which are often excessive during ketamine anaesthesia. Patients in both groups were

given pancuronium 0.01 mg·kg^{-1}; and fentanyl 100–150 μg, dependent on body weight, five minutes before the induction of anaesthesia.

Anaesthesia was induced with an infusion of 0.5 ml·kg^{-1}·min^{-1} of a ketamine-benzodiazepine solution. One half of the patients received infusion from a solution of ketamine 250 mg and diazepam 20 mg in 250 ml of 0.9 per cent NaCl. The other half received infusion from a solution of ketamine 250 mg and midazolam 12.5 mg in 250 ml of 0.9 per cent NaCl. When the patients did not answer on command, and the ciliary reflex was absent, the patients were given succinylcholine 1.5 mg·kg^{-1} to facilitate tracheal intubation. Anaesthesia was maintained with the ketamine-benzodiazepine infusion, and fentanyl was administered in increments of 50–100 μg in accordance with the heart rate and blood pressure. The neuromuscular block was maintained with an infusion of succinylcholine. The anaesthesia was totally intravenous, the patients being ventilated with 100 per cent oxygen.

During anaesthesia arterial blood pressure and heart rate were monitored every fifth minute and more often when necessary. All the patients were anaesthetised by the same anaesthetist (one of the investigators), who adjusted the infusion rate and gave fentanyl in accordance with the heart rate and blood pressure. Postoperatively the patients were observed by one of the investigators for any vocalisation or movements that could indicate a phase of dreaming. In the presence of severe postoperative emergence reactions, the nursing staff were able to contact a consultant who was independent of the investigators. This consultant could break the code and give the patient either diazepam 5 mg IV or midazolam 3 mg IV in such a way that every patient continued with the same benzodiazepine.

Time t_1 was the time when the patients were able to give their correct name, date of birth, name of the hospital and to lift the right thumb on command. Patients who received benzodiazepines during the awakening period were excluded from the investigation of t_1 and t_2, but still included in the investigation of emergence reactions. Time t_2 was the time when the patients subjectively felt completely awake, in such a way that they could leave the hospital. Before leaving the hospital the patients were asked by one of the investigators if they had experienced any dreaming, visual disturbances, or awareness during the anaesthetic, and if they would want the same anaesthetic again.

The differences between the two groups were analysed using Student's t test. For non-parametric data the χ^2 test was used and for t_2 Wilcoxon's rank sum test was applied.

Results

The two groups were comparable with regard to age, sex, weight, height and type of operation performed (Table I). There was no significant different in doses of ketamine, fentanyl or succinylcholine between the two groups (Table II). There was no difference between the t_1 awakening times ($p > 0.05$). The t_2 awakening time was more than doubled in the diazepam group ($p < 0.01$). Two patients in the diazepam group did not feel completely recovered from the anaesthetic when they left the hospital, the day after surgery.

There was a significantly higher frequency of emergence reactions in the diazepam group ($p < 0.01$), and on five occasions it was necessary to give supplementary diazepam to calm the patients (Table III). In the midazolam group only one patient had a slight emergence reaction. Two patients in the diazepam group experienced dreams during anaesthesia, while this was not reported in the midazolam group. Two patients in the diazepam group stated they would not want the same anaesthetic again. One patient experienced 48 hours of amnesia postoperatively, the second had unpleasant dreams. All the patients in the midazolam group were satisfied with the anaesthetic they had received. No awareness during anaesthesia was reported in either group. There was no difference in the mean heart rates and arterial blood pressures in the two groups, either preoperatively or intraoperatively (Table

TABLE I Patient data. Number of patients and mean values ± SEM

	Diazepam + ketamine	*Midazolam + ketamine*
No. of patients	25	25
Sex (M:F)	12:13	15:10
Age (years)	52.8 ± 3.5	53.5 ± 3.3
Weight (kg)	74.3 ± 4.8	76.4 ± 2.4
Height (cm)	169.2 ± 1.8	173.6 ± 1.5

TABLE II Duration of anaesthesia, doses of ketamine, fentanyl, succinylcholine and awakening times t_1 and t_2. Mean ± SEM

	Diazepam + ketamine	*Midazolam + ketamine*	*p value*
Duration of anaesthesia (minutes)	52.8 ± 8.1	47.2 ± 7.7	NS
Dose of ketamine (mg)	217.2 ± 17.5	187.6 ± 8.5	NS
Dose of fentanyl (μg)	186.0 ± 17.5	158.0 ± 10.0	NS
Dose of succinylcholine (mg)	394.0 ± 44.3	327.2 ± 38.9	NS
t_1 (minutes)	96.2 ± 18.9	72.8 ± 5.6	NS
	n = 20	n = 25	
t_2 (hours and minutes)	16h46m	8h15m	p < 0.01
	n = 20	n = 25	

NS (nonsignificant). (For t_2 SEM is not recorded as the results are not normally distributed)

TABLE III Number of patients with emergence reactions, visual disturbances (blurred vision or diplopia) and with a memory of dreaming

	Diazepam + ketamine	*Midazolam + ketamine*	*p value*
Emergence reactions	9	1	$p < 0.01$
Mild	4	1	
Severe	5	1	
Dreaming	2	0	NS
Good	1	0	
Bad	1	0	
Visual disturbances	3	3	NS

χ^2 test. NS (nonsignificant).

IV). None of the patients complained of pain at the injection site when the ketamine-benzodiazepine infusion was started.

Discussion

Our results show that the combination of midazolam and ketamine was not followed by a significantly shorter t_1 awakening time compared to diazepam and ketamine. This can be explained by the fact that diazepam's distribution half-life $t_1\alpha$ (30–60 minutes) is only slightly longer than $t_1\alpha$ for midazolam (15 minutes).[9] The time until the patients subjectively felt completely awake after the anaesthesia, t_2, was significantly shorter in the midazolam group. Midazolam has a much shorter elimination half-life $t_1\beta$ (1.5–3.5 hours) whereas diazepam has a very long $t_1\beta$ (20–99 hours).[9] The two patients who did not feel fully recovered the day after surgery, and the patient who experienced a 48-hour period of amnesia postoperatively, had received diazepam.

We compared diazepam and midazolam in a ratio of 1.6:1, which is within the range of doses that other investigators have regarded as equipotent. Ketamine's $t_1\alpha$ (7–11 minutes) and $t_1\beta$ (120–180 minutes)[4] are similar to the midazolam half-lives, which suggests that midazolam is a more logical adjuvant to ketamine than diazepam, with a view to recovery time. A midazolam-ketamine infusion is therefore preferable, especially for operations after which the patients are leaving the hospital on the day of, or the day after surgery.

Cartwright and Pingel[8] gave a single dose of benzodiazepine before the ketamine injection and found that midazolam was more effective in reducing bad dreams but did not offer any advantage in reducing emergence reactions. We anaesthetised our patients with a continuous infusion of ketamine-benzodiazepine, with small increments of fentanyl, and found a much lower frequency of dreaming. In fact, we did not find a single case of dreaming in patients who had received the midazolam-ketamine infusion. Whether it is possible to avoid dreaming completely by using this modified ketamine anaesthetic must await further investigation. Our results show that midazolam is more effective than diazepam in reducing dreaming associated with ketamine. We also found that midazolam was significantly better in reducing emergence reactions. Emergence reactions are not necessarily associated with a memory of dreaming, but they are very distressing to relatives and nursing staff.

A major problem associated with total intravenous anaesthesia is the possibility of awareness.[9] We did not observe a single case of awareness.

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TABLE IV Mean systolic and diastolic blood pressures and mean heart rates ± SEM

Time (minutes)	*0*	*10*	*20*	*30*	*40*	*50*	*60*
Systolic BP							
Diazepam	135.9 ± 5.0	173.5 ± 5.8	162.4 ± 6.0	157.4 ± 6.0	146.2 ± 5.6	140.0 ± 7.7	136.0 ± 6.0
Midazolam	142.6 ± 4.7	189.1 ± 6.8	156.0 ± 5.6	145.3 ± 4.8	138.2 ± 4.6	138.0 ± 4.5	138.0 ± 4.9
Diastolic BP							
Diazepam	77.3 ± 2.6	102.9 ± 4.3	95.3 ± 3.3	88.8 ± 3.8	85.6 ± 3.6	81.0 ± 4.8	80.8 ± 4.5
Midazolam	83.6 ± 3.9	101.5 ± 4.2	92.6 ± 3.5	90.0 ± 3.6	80.7 ± 3.0	80.5 ± 3.9	81.0 ± 1.9
Heart rates							
Diazepam	82.3 ± 4.2	101.5 ± 3.5	90.4 ± 3.5	88.3 ± 2.9	88.3 ± 3.6	89.1 ± 4.8	86.9 ± 6.5
Midazolam	76.9 ± 4.3	94.9 ± 4.8	86.7 ± 4.0	86.8 ± 3.2	84.4 ± 3.2	78.8 ± 5.0	70.0 ± 5.8

P = NS

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Résumé

Une étude prospective à double insu a été faite chez cinquante patients anesthésiés par voie veineuse seulement, pour endoscopie (laryngoscopie, bronchoscopie, médiastinoscopie). La moitié des patients ont été anesthésiés avec une solution de 250 ml de kétamine et de 12.5 mg de midazolam par infusion. L'autre moitié a reçu une solution de 250 mg de kétamine et de 20 mg de diazépam par infusion. De plus, les deux groupes ont reçu des doses croissantes de 50–100 µg de fentanyl. Le temps de réveil immédiat (t_1) n'était pas significativement plus court chez les patients ayant reçu du midazolam-kétamine, mais, chez ces patients, le temps de rétablissement plus complet était significativement plus court (t_2) la fréquence des réactions à l'émergence était significativement plus basse et ces patients étaient plus satisfaits de l'anesthésie que les patients qui avaient reçu du diazépam-kétamine. Il n'y pas eu de différence entre les groupes en ce qui a trait à la fréquence cardiaque et à la tension artérielle intraopératoire. On a rapporté aucune reprise de conscience durant l'anethésie.