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Comparison of sedation with midazolam and ketamine: effects on airway muscle activity†

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Summary

Male patients, aged 27–74 yr, without hypertension or overt cardiovascular disease were premedicated with temazepam 20 mg orally and allocated randomly to receive sedation with either midazolam (12 patients) in a dose sufficient to provide light sedation (retained response to loud voice) or ketamine 1 mg kg^{-1} (11 patients). Median midazolam dose was 0.08 (interquartile range 0.02) mg kg^{-1}. The activity of the muscles of the tongue, anterior neck and scalene group was measured with surface electrodes and compared with the awake state. Muscle activity decreased significantly after midazolam in each group of muscles, to median values of 42 %, 28 % and 33 %, respectively, of awake values. Airway obstruction occurred in 10 of 12 patients and during obstruction muscle activity increased significantly to 69 %, 73 % and 52 % of awake values, but in all cases this was insufficient to overcome the obstruction. After ketamine, activity did not change significantly and there were no episodes of airway obstruction. Phasic muscle activity was noted after sedation in 11 subjects but there was no difference in the incidence between the two groups (midazolam, six patients; ketamine, five patients). (*Br. J. Anaesth*. 1996; **76**: 663–667)

Key words

Hypnotics benzodiazepine, midazolam. Anaesthetics i.v., ketamine. Airway, muscles.

Sedation is used frequently in association with regional anaesthesia during surgery [1], and for procedures such as endoscopy [2]. Respiratory function is impaired frequently by sedation [3, 4] and sedation is associated with serious adverse events [5]. Sedative agents such as barbiturates [6] and benzodiazepines [7] cause loss of airway muscle tone and an increase in airway resistance [8]. Ketamine, which is a potential sedative for patients undergoing surgery with regional anaesthesia, appears to have less profound effects on the muscles of the upper airway [9]. In this study, we compared the effects of sedation with midazolam and ketamine on upper airway and respiratory muscles in men undergoing anaesthesia. Men were chosen as they seem to have more problems than women with airway patency in association with sedative use [10, 11]. We also investigated the effects of airway obstruction on airway muscle activity and the incidence of phasic patterns of activity of the muscles.

Subjects and methods

After obtaining approval from the local Ethics of Medical Research Committee and informed consent, we studied male patients undergoing routine surgical procedures under general anaesthesia. Patients were recruited if they had no overt cardiovascular or respiratory disease, and had a normal arterial pressure. Exclusion criteria were age more than 75 yr, body weight more than 120 % of that expected for height and weight, obvious risk of regurgitation and those receiving sedative or analgesic medication or treatment for hypertension. Subjects were allocated randomly to receive either midazolam or ketamine by random number tables.

After an overnight fast, premedication comprised temazepam 20 mg orally, 1 h before the patient was studied. The study room was kept warm and quiet and patients were encouraged to relax as much as possible. During local anaesthesia, an i.v. cannula was inserted and a slow infusion of 0.9 % saline was started through an infusion set fitted with an extension to allow drug administration without the knowledge of the patient.

Electrocardiograph electrodes were attached and the ECG displayed continuously. Non-invasive arterial pressure measurements were not obtained regularly because they could disturb the patient. The patient lay in the supine position with the head supported in a neutral position in the midline on a single soft pillow. The arms were supported at the sides and the recording apparatus was kept out of the line of vision of the patient.

EMG activity was recorded as in a previous study [6]. Briefly, the skin surface was prepared to obtain an inter-electrode resistance of <2 kΩ. Disposable pre-gelled silver–silver chloride electrodes were placed with centres 3 cm apart, in the midline posterior to the lower edge of the mandible (tongue), just below the thyroid prominence (neck strap muscles) and over the right scalenus medius (scalene group), and recorded with the ECG using an FM

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tape recorder. In subsequent analyses the signals were rectified and integrated with a time constant of 100 ms after gating to remove the ECG component [12]. Recordings were made over at least 30 s. Maximum amplitude of the integral during the respiratory cycle was measured. The presence of phasic activity was classified as a variation in amplitude within the respiratory cycle of more than 50 % peak activity, during episodes when airway obstruction was judged to be minimal.

After attaching the electrodes, patients were encouraged to relax for at least 5 min without speaking before measurements were made of resting awake activity. Midazolam was given as an initial bolus of either 2 or 3 mg, according to age, and then in 1-mg or 0.5-mg doses at 3-min intervals to obtain a sedated state where the eyelids were drooping but not shut (the patient would respond either to a voice or light touch to the face) and the eyelash reflex was present.

Ketamine 1 mg kg^{-1} was given as a single dose. After administration the patients were not spoken to unless absolutely necessary, and given no specific instructions either to open or close the eyes. The ambient noise in the room was kept as small as practicable. Measurements were made 3 min after the last dose of midazolam, and at 2 and 4 min after administration of ketamine to provide some indication of the rate of onset of activity of this agent. In patients who received midazolam, further measurements were made during episodes of partial or complete airway obstruction and in some subjects, where possible, after relief of the obstruction by gentle support of the jaw or backward tilting of the head to obtain a clear airway with minimal arousal of the patient. The presence of airway obstruction was judged by clinical criteria, such as changes in gas flow felt at the mouth and nose, noise of breathing and pattern of chest and abdominal motion. In addition, in some patients changes in the movement of mouth and lips were noted. If the obstruction appeared severe, it was always remedied after 1 min. After measurements of muscle activity, administration of oxygen was started and anaesthesia was induced. After induction of anaesthesia and neuromuscular block, another recording of electrical activity was made to allow an exact measure of background electrical activity which was subtracted from the integral values.

Data were analysed using a spreadsheet (Excel v 5.0a) and a statistics package (Minitab release 8.2) using MS-DOS 6.2. Values are given as median (quartiles). Muscle activity, expressed as a percentage of the awake value, was converted to logarithms before statistical comparison; within subjects using the Wilcoxon test and between groups using the Mann–Whitney test. The incidence of phasic muscle activity was compared between groups with Fisher's exact test.

Results

The groups were comparable in age (53, 42–62 *vs* 64, 57–67 yr), height (178, 171–179 *vs* 175, 168–180 cm), weight (71, 63–75 *vs* 67, 61–83 kg) and weight as a percentage of expected weight (95, 90–108 % *vs* 103, 93–114 %) (respective values for midazolam and ketamine).

Table 1 Muscle activity (% of awake values) in the two groups, during periods when airway obstruction was judged to be minimal. Values are median (quartile) values

	Midazolam	Ketamine
Muscle group		
Tongue	42 (20–44)	72 (60–155)
Strap muscles of neck	28 (19–60)	175 (130–213)
Scalene muscle	33 (19–62)	100 (81–311)

The 12 patients who received midazolam were given a median dose of 5 mg (seven patients received 5 mg; dose range 3–8; quartiles 5 and 7 mg). In all patients the required end-points of sedation were reached and no patient was judged to have become oversedated. Airway obstruction occurred in 10 patients sedated with midazolam and patients were either repetitively aroused or the jaw was supported to restore airway patency. In another patient, breathing became noisy but there was no obstruction.

One patient received midazolam 8 mg, which was the largest dose required. If this patient is excluded, there was a significant decrease in dose requirements with age ($P < 0.05$), although the correlation was not strong ($r = 0.4$), indicating considerable variation in dose requirements, independent of age. The relationship between dose and age was less significant if the dose was considered in terms of actual or ideal body weight, although there was no relationship between body weight and age.

There was no difference in muscle activity at 2 and 4 min after administration of ketamine, and the 4-min measurements have been used for presentation and analysis. After ketamine, all patients became quiet and detached. None had clinically apparent airway obstruction.

Sedation with midazolam was associated with a significant reduction in muscle activity in all three muscle groups ($P < 0.01$), whereas there was no significant change in activity after ketamine (table 1).

Partial or complete airway obstruction developed in 10 of 12 patients who received midazolam. In all subjects there were changes in the sounds of airflow, and reductions in gas flow palpable at the airway opening. In six subjects there were changes in the pattern of movement of lips, cheeks, the suprahyoid region of the neck and the chest wall, particularly as the obstruction was prolonged. In patients who received midazolam, measurements during airway obstruction showed progressive increases in muscle activity that were more obvious in the strap muscles of the neck and the scalenes, although there were no significant differences in the increases in the three groups. A typical example is shown in figure 1 and the changes in all subjects are shown in figure 2. During episodes of airway obstruction, activity was phasic in two, six and seven subjects in the tongue, neck strap muscles and scalene muscles, respectively. When the obstruction was relieved, successful recording of activity was obtained in five subjects. In all of these subjects airway muscle activity decreased

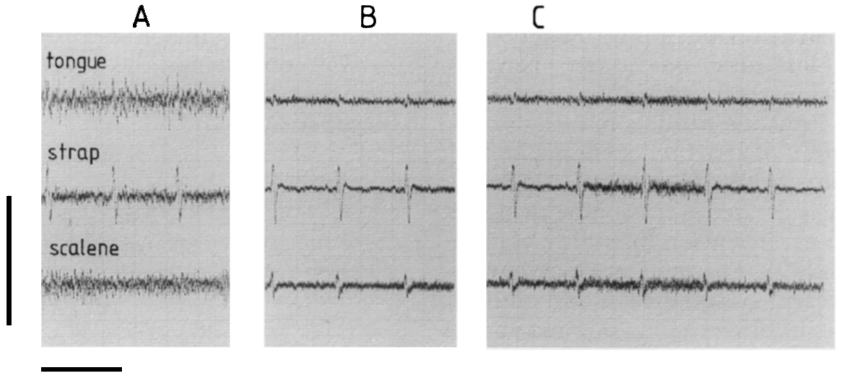

Figure 1 Representative recording of EMG signals in a patient who received midazolam. A = Awake; B = after sedation; and C = during an episode of partial airway obstruction. There is a marked reduction in tonic activity after sedation and an increase in phasic activation in time with inspiration during partial airway obstruction. (Vertical scale marker = 1 mV, horizontal scale marker = 1 s.)

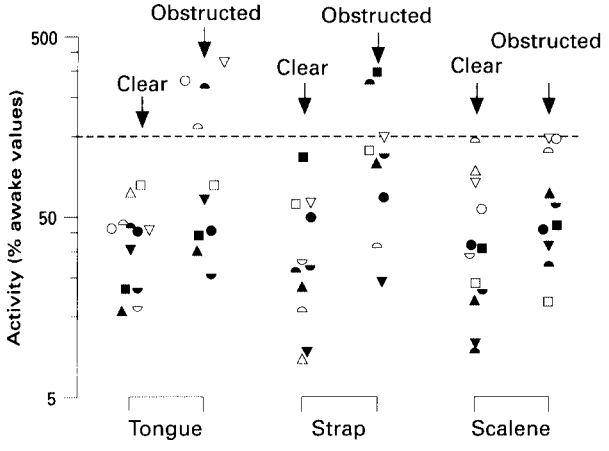

Figure 2 Changes in the activity of the three muscle groups (expressed as percentage of awake values) in patients sedated with midazolam, during episodes of clear breathing (all subjects) and obstructed breathing attempts (10 subjects). The dotted horizontal line indicates the awake activity. Each subject is shown by a different symbol. For subjects with airway obstruction, the increase in activity in each muscle group was significant ($P < 0.05$). Note that obstruction persisted despite activity in some patients being greater than the awake value.

considerably but there were insufficient numbers to allow statistical analysis of sufficient power by the Wilcoxon test.

There was evidence of phasic activity in five patients after ketamine sedation, but in only one subject was phasic activity seen in the tongue signal.

There were no adverse events in the study apart from episodes of airway obstruction, which were corrected promptly. No patient reported unpleasant experiences. The quality of recovery from the subsequent anaesthesia was not altered discernibly.

Discussion

Comparison of sedation with midazolam and ketamine is not simple. In clinical terms, the states of sedation were comparable. However, the ED_{95} for abolition of response to command by ketamine is approximately 0.6 mg kg^{-1} [13], and therefore the dose chosen in this study may have been larger than necessary. In contrast, the end-point of midazolam sedation was deliberately "light" and several patients became aroused by the manoeuvres used to restore airway patency. In patients who received midazolam it is also likely that there was considerable interaction between the drug effect and the sleep state. Such interactions may perhaps explain the discrepancies in previous results where airway obstruction was not observed after the use of similar or greater doses than in the present study [1, 4]. Another factor that complicates comparison between studies is the variation in susceptibility to midazolam with age [14]. The relative potencies of these two agents depend on the measure of effect that is used for comparison as they do not have parallel dose–response relationships [13]. The dose of midazolam relative to ketamine used in this study was less than the equivalent dose in a previous comparison [15], but the patients in that study were less healthy (ASA III or IV). In addition, in our study patients were premedicated with temazepam. This is likely to have had an additive influence on the effects of midazolam. For ketamine, which is a different class of agent, the effects are less easy to predict, but ketamine appears to have additive effects with propofol (which does act in a way similar to that of the benzodiazepines) [16]. Stella, Torri and Castiglioni [13] reported that the ED_{95} of ketamine for abolition of response to command was 0.6 mg kg^{-1} and for diazepam, which is generally considered to be approximately 50 % as potent as midazolam, 0.5 mg kg^{-1}, which again suggests that the dose of midazolam used in this study was small in comparison with the dose of ketamine.

Additional measurement of airway or oesophageal pressure would have allowed more exact assessment of the relationship between muscle action, airway pressure and resistance changes. However, such measurements are more invasive and more likely to alter arousal and consequent responses than the presence of external electrodes. On the other hand, inductance band measurements of the rib cage and abdomen would have caused no disturbance to patients and might have confirmed previous observations of the pattern of rib cage movement during sedation with midazolam [17] which have now been recognized as associated with airway obstruction [11].

The pattern of activity in the muscles studied was similar to that found in a previous study [6], although tongue activity was less often phasic than activity recorded using intramuscular electrodes placed via the mouth [18, 19]. Previous workers have reported variations in the pattern of activity depending on the site of measurements [20]. In normal subjects, genioglossus activity is greater in the supine than the sitting position, and greater when breathing via the nose than the mouth [19]. These factors may have a bearing on the present results as from clinical experience and previous observations [6], increasing sedation alters the route of respiration from the nose to the mouth, probably with loss of muscle tone in the soft palate, and a change in the breathing route may contribute to loss of tongue muscle activity. Our observations of scalene muscle activity are also in agreement with previous reports [6, 21–23] but not with a more recent study using intramuscular electrodes [24] in which no activity was found during quiet respiration in the supine position.

In this study, administration of ketamine was not associated with loss of airway patency or with a decrease in airway muscle activity, consistent with previous animal studies [9]. Previous studies in humans with ketamine 1 mg kg^{-1} reported greater resistance to aspiration of radio-opaque markers than with other sedatives such as diazepam [25]. In contrast, there was marked loss of airway muscle activity and airway patency with administration of midazolam. Animal studies in particular indicate the relative importance of the neck muscles in the control of airway patency [26, 27].

Sedation with midazolam 0.1 mg kg^{-1} increases nasal airway resistance in supine subjects [8] and causes a reduction in inspiratory flow and snoring in male, or female, subjects with partial nasal obstruction [11]. The obstruction causes an increase in the relative contribution of the rib cage to respiratory movement [11, 17] which suggests reflex activation of rib cage muscles such as the scalenes, which can contribute to rib cage movement [28–31], and is consistent with our observations. Such abnormalities of movement in sedated patients can be reversed by application of positive airway pressure [32].

The progressive increase in activation of the muscles during obstruction has been noted in previous studies [18] but does not appear to be a universal finding in sleeping patients. The mechanism is unclear. Although there are reflexes associated with upper airway sensation [33–35], and in animals from lung volume feedback [36], there is also a progressive increase which resembles the probable increase in chemical drive. It is possible that arousal from the sedated state might have occurred if the airway muscle activity had been allowed to increase further, as occurs in sleep apnoea [37].

This study suggests that when male patients are sedated with midazolam, even if they remain easily rousable, close attention must be paid to their airway, and airway support is likely to be required. In contrast, ketamine sedation is not likely to reduce airway muscle activity and impair upper airway patency. The results of this study, together with previous studies [11, 17], also suggest that observation of movements of the rib cage may be misleading in the assessment of the presence of airway obstruction, as most observers probably associate breathing difficulty with reduced rib cage excursion.

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