Sedation for upper gastrointestinal endoscopy: a comparison of alfentanil-midazolam and meperidine-diazepam

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The authors studied the efficacy and cost of substituting sedation using midazolam and alfentanil for the existing regimen of diazepam and meperidine in patients requiring upper gastrointestinal endoscopy. Sixty consenting subjects were randomized to receive either meperidine 50 mg with diazepam approximately $90 \mu\text{g} \cdot \text{kg}^{-1}$ (Group D) or alfentanil 250 μg with midazolam approximately $50 \mu\text{g} \cdot \text{kg}^{-1}$ (Group M). Endoscope insertion time, patient acceptance, apnoeic or desaturation episodes were noted by a physician observer. Pulse oximetry was used to monitor heart rate and oxygen saturation (SpO_2) during endoscopy. Subjects performed four-choice reaction time (4CRT) tests before, 30 and 60 min after endoscopy, and were assessed for nausea or dizziness and their ability to stand and walk. During endoscopy, insertion time was shorter (84 ± 45 sec vs 122 ± 83 sec, $P < 0.03$) and fewer aversive movements occurred (0.4 ± 0.6 vs 1.7 ± 2.4 , $P < 0.005$) in Group M than Group D. No subject in either group suffered any apnoea or prolonged desaturation requiring supplemental oxygen. Irrespective of treatment group, greater decreases in SpO_2 ($6.1 \pm 3.4\%$ vs $3.6 \pm 2.2\%$, $P < 0.001$) occurred in subjects >45 yr of age than in subjects ≤ 45 yr. During recovery 4CRT values at 30 min after endoscopy were longer (723 ± 226 msec vs 594 ± 139 msec, $P < 0.005$) in Group M than in Group

D but not after 60 min. It was concluded that the small differences in endoscopy conditions and greater sedation during the first 30 min of recovery did not justify the additional cost of using midazolam and alfentanil.

Les auteurs comparent l'efficacité et le coût de la substitution du midazolam et de l'alfentanil utilisés pour la sédation à l'association courante de diazepam et de mepéridine chez des patients soumis à un endoscopie gastro-intestinale haute. Soixante adultes consentants sont répartis au hasard pour recevoir soit mepéridine 50 mg avec diazepam $90 \mu\text{g} \cdot \text{kg}^{-1}$ environ (groupe D) soit alfentanil 250 μg avec $50 \mu\text{g} \cdot \text{kg}^{-1}$ environ de midazolam (groupe M). Le temps requis pour d'introduction de l'endoscope, le degré d'acceptation par le patient, la durée des périodes d'apnée et de désaturation sont enregistrés par un observateur médecin. L'oxymétrie pulsée est utilisée pour monitorer la fréquence cardiaque et la saturation en oxygène (SpO_2) pendant l'endoscopie. Les sujets sont évalués par un test de vitesse de réaction à quatre choix (4CRT), avant, 30 et 60 min après l'endoscopie et en rapport avec la nausée, les vertiges et l'habileté à la station debout et à la marche. A l'endoscopie, la durée de l'introduction est plus courte (84 ± 45 sec vs 122 ± 83 sec, $P < 0,03$) et les mouvements involontaires moins fréquents ($0,4 \pm 0,6$ vs $1,7 \pm 2,4$, $P < 0,005$) dans le groupe M que dans le groupe D. Dans les deux groupes, aucun des sujets ne souffre d'apnée et de périodes de désaturation prolongées nécessitant un supplément d'oxygène. Indépendamment du groupe, les baisses plus importantes de SpO_2 ($6,1 \pm 3,4\%$ vs $3,6 \pm 2,2\%$, $P < 0,001$) surviennent plus souvent chez les sujets de plus de 45 ans que chez ceux de moins de 45 ans. A la période de récupération postendoscopique, les valeurs du 4CRT à 30 min sont plus longues (723 ± 226 msec vs 594 ± 139 msec, $P < 0,005$) dans le groupe M que dans le groupe D, ce qui disparaît à 60 min. En conclusion, la petite différence notée pour les conditions de l'endoscopie et pour la sédation plus importante des 30 premières min de la récupération ne justifient pas le coût additionnel du midazolam et de l'alfentanil.

Key words

ANAESTHESIA: sedation;

ANALGESICS: alfentanil meperidine;

HYPNOTICS: benzodiazepines, midazolam, diazepam;

SURGERY: endoscopy.

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Upper gastrointestinal endoscopy using topical anaesthesia alone is poorly tolerated¹ and may result in reduced patient attendance at follow-up procedures. The ideal sedative for endoscopy would be highly anxiolytic and amnesic, suppress gag reflex without respiratory depression, have a rapid onset, short predictable duration of action and rapid elimination. Midazolam has a rapid onset, is redistributed twice as rapidly and eliminated ten times as quickly as diazepam after a single bolus dose.² Midazolam and diazepam have been studied extensively as sedative agents for upper gastrointestinal endoscopy. Midazolam with topical anaesthesia alone has been shown to provide superior patient amnesia, acceptance of endoscope insertion, and a lower incidence of thrombophlebitis than diazepam.^{3,4}

Narcotic-benzodiazepine combinations produce better operating conditions than benzodiazepines alone and reduce the dose of benzodiazepines required.⁵⁻⁷ Narcotics reduce the individual subject's variability of response to midazolam.⁸ It is also known that meperidine increases the ventilatory depression caused by midazolam and diazepam.⁹ The interaction of sedation and respiratory depression has been held responsible for an increased incidence of complications during and after endoscopy.¹⁰⁻¹² Alfentanil is 90% un-ionized at pH 7.4, has a greater lipid solubility than meperidine and dissociates rapidly from analgesic receptors. It also has an elimination half-life approximately half that of meperidine.¹³ These properties give alfentanil the fastest onset and the shortest duration of action of all clinically available opioids. We have compared the effect of midazolam and alfentanil on patient sedation, endoscopy conditions, heart rate, arterial saturation, recovery of psychomotor performance and cost of medication under clinical conditions similar to those currently used to administer diazepam and meperidine.

Methods

With institutional ethics committee approval and individual informed consent, 60 patients undergoing elective upper GI endoscopy were admitted to the study. Exclusion criteria were pregnancy, chronic obstructive pulmonary disease or hepatic cirrhosis. Each subject was randomized to one of the two treatment groups (Group D or Group M) using a random number table. Following patient orientation and baseline data collection, a pulse oximeter (Nellcor N-100, Hayward, CA) probe was attached. Nasal oxygen prongs were fitted but oxygen was not administered unless SpO₂ decreased below 90% for at least 30 seconds. Topical lidocaine 10% 50 mg was sprayed into each subject's oropharynx. Group M patients then received alfentanil 0.250 mg *iv* followed by midazolam 2.5, 3.75 or 5.0 mg *iv* according to weight

TABLE I Dosage scale for diazepam (Group D) and midazolam (Group M)

Weight (kg)	Diazepam (mg)	Midazolam (mg)
<50	5.0	2.5
50-99	7.5	3.75
>99	10.0	5.0

(Table I). Patients in Group D were given meperidine 50 mg *iv* followed by diazepam 5.0, 7.5 or 10.0 mg *iv* using similar criteria. After dilution to equivalent volumes in masked syringes by the anaesthetist-observer, the drugs were administered by bolus injection via an antecubital vein by the endoscopist (DSD), who was unaware of which drugs were being used. Endoscope insertion commenced at the onset of dysarthria according to established practice.

Pre-sedation arterial oxygen saturation (SpO₂) and pulse rate were obtained from the pulse oximeter and recorded by the attending anaesthetist. The times of drug administration, endoscope insertion and removal and maximum pulse rate, lowest SpO₂, any aversive movements or apnoeic episodes were noted for each 30 sec interval. Apnoea was defined as the absence of coordinated respiratory effort over a 15 sec period. Operating conditions were graded as good, satisfactory or poor by the endoscopist.

Before the procedure, each subject performed psychomotor testing using a portable four-choice reaction time (4CRT) apparatus (Kneesworth Ltd, Cambridge, UK).¹⁴ Patients were requested to respond to a series of stimuli, consisting of one of four light-emitting diodes illuminated in random order, by pushing the appropriate key. Reaction time and appropriateness of each response was recorded on cassette tape for later analysis. One practice test was performed before baseline data collection and endoscopy. At 30 and 60 min after endoscopy, subjects were asked to sit, stand and walk, were questioned about the presence of dizziness or nausea and underwent repeat 4CRT testing.

For each 4CRT test, summary statistics derived were mean reaction time and total number of errors. Test data with greater than 15% error rates were discarded. Multivariate repeated measures analysis of variance (CSS Statistica, Statsoft) were used to compare the effect of treatments and times on 4CRT variables. When appropriate, Duncan's multiple range test was used to compare the differences between individual mean values. Other continuous variables were compared using Student's *t* test (BMDP7V, BMD Statistical Software); the independence of categorical variables was tested using chi-square with Yates' correction (BMDP4F).

TABLE II Characteristics of study population. Where appropriate, values are mean $\pm$ SD

	Group D (n = 30)	Group M (n = 30)
Male/female	12/18	12/18
Age (yr)	46.0 $\pm$ 16.6	51.6 $\pm$ 13.2
Weight (kg)	70.5 $\pm$ 12.9	72.9 $\pm$ 21.8
Concurrent benzodiazepines	4	7
Baseline pulse rate (bpm)	80.9 $\pm$ 12.2	80.6 $\pm$ 13.0
Baseline SpO ₂ (%)	96.9 $\pm$ 1.8	96.7 $\pm$ 2.1
Control 4CRT (msec)	575 $\pm$ 129	657 $\pm$ 200*

*Indicates Group M significantly ($P = 0.001$) greater than Group D.

Results

The two groups were similar with respect to age, weight, sex, and numbers taking concurrent benzodiazepine therapy (Table II). Baseline values for pulse rate and SpO₂ did not differ significantly (Table II). Mean dose ($\pm$ SD) of diazepam used was $91 \pm 12 \mu\text{g} \cdot \text{kg}^{-1}$ and of midazolam was $47 \pm 6 \mu\text{g} \cdot \text{kg}^{-1}$.

Endoscopy procedure

Endoscope insertion time was shorter and the incidence of aversive movement lower in Group M (Table III). There were no differences in total operating time or time to orientation (Table III). Operating conditions were rated excellent or good in the majority of patients in both groups. The proportion of patients in whom endoscopic conditions were rated poor was 5/30 in Group D and 0/30 in Group M which was not a significant difference ($P = 0.053$). No apnoeas or desaturations lasting ≥ 30 sec occurred in either group. Highest pulse rate and lowest SpO₂ did not differ between the two groups.

Division of subjects into groups *post hoc* based on age (>45 yr and ≤ 45 yr) showed that the lowest SpO₂ was higher and the decrease in SpO₂ (the difference between awake baseline and the nadir) was less in the younger age group irrespective of which sedation was used (Table IV).

Recovery from sedation

Valid 4CRT results were obtained for 58 subjects, 29 in each group. One subject was eliminated because the quality of the recording was inadequate for decoding, the other because of a control response error rate greater than 25% which probably indicates a failure to understand the test instructions. Group M subjects tended to have a longer mean control 4CRT than Group D, 657 ± 200 and 575 ± 129 msec respectively ($P = 0.001$). Thirty minutes after endoscopy, mean reaction times had increased ($P = 0.0078$) to 724 ± 262 msec in Group M but were unchanged at 594 ± 139 msec in Group D. After 60 min

TABLE III Values (means $\pm$ SD) of some outcome variables

	Group D (n = 30)	Group M (n = 30)
Insertion time (sec)	122.1 $\pm$ 82.8*	84.0 $\pm$ 45.0
Finish time (sec)	423.3 $\pm$ 255.9	359.2 $\pm$ 252.6
Time to orientation (sec)	448.1 $\pm$ 264.6	372.6 $\pm$ 263.8
Maximum pulse rate (bpm)	92.2 $\pm$ 17.6	88.0 $\pm$ 13.8
Nadir SpO ₂ (%)	92.0 $\pm$ 3.4	91.3 $\pm$ 4.4
Aversive movements	1.7 $\pm$ 2.4†	0.4 $\pm$ 0.6
Reaction time change after 30 min recovery (% control) (n = 29)	3.6 $\pm$ 23.0	10.3 $\pm$ 9.3
Reaction time change after 60 min recovery (% control) (n = 29)	-2.8 $\pm$ 12.6	-6.8 $\pm$ 13.1

*($P < 0.03$) and †($P < 0.005$) indicates Group D mean value significantly greater than Group M.

TABLE IV Observed lowest and decrease, baseline-nadir, in SpO₂ (%). Values are mean $\pm$ SD

	Age ≤ 45 (n = 23)	Age > 45 (n = 37)
Lowest SpO ₂	94 $\pm$ 2.9	90 $\pm$ 3.7*
SpO ₂ decrement	3.6 $\pm$ 2.2	6.1 $\pm$ 3.4*

*Indicates differs significantly ($P < 0.001$, t test independent groups) from age ≤ 45 yr.

recovery 4CRT decreased in Group M to 606 ± 182 msec which was not different from either control value or Group D (553 ± 118 msec). There were no differences in the number of errors per test. At the end of the study, 60 min after endoscopy, three Group D subjects were unable to stand and walk across the room without assistance whilst none of the Group M subjects needed help; however, this difference was not statistically significant ($P = 0.24$). Four Group D subjects reported nausea 30 mins after endoscopy and two in Group M. Six Group D subjects and four Group M reported dizziness when trying to stand 30 min after endoscopy. No subjects in either group were dizzy or nauseous at 60 min.

Discussion

In this otherwise healthy, predominantly middle-aged patient group, a more rapid onset of clinical sedation and fewer aversive movements were noted following midazolam/alfentanil (Group M) compared with diazepam/meperidine (Group D). The time to ambulation or discharge was not prolonged. The results of the 4CRT test 30 min after endoscopy suggest that Group M suffered greater early residual sedation. However, the average relative impairment was only a 10% increase in reaction time compared with presedation control. Moreover, 60 min after endoscopy, Group M subjects performed as well as Group D and control. The difficulty of designing

psychomotor tests of adequate sensitivity to detect residual effects of sedatives or anaesthetics is well recognized.¹⁵ Choice reaction time has been shown to be adequate to detect the residual effects of midazolam 15 mg for up to 5 hr¹⁶ and anaesthesia in surgical patients for up to eight hours.¹⁴

Our results are consistent with several previously reported studies. Magni *et al.* compared meperidine/diazepam with meperidine/midazolam. Both groups received 50 mg meperidine followed by incremental doses of either diazepam or midazolam until clinically sedated. The average initial dose of midazolam was $110 \mu\text{g} \cdot \text{kg}^{-1}$ and of diazepam $170 \mu\text{g} \cdot \text{kg}^{-1}$ and approximately one-third of the subjects underwent ERCP for which they received hyoscine and often additional sedation. These doses which were approximately twice the amount used in our study produced greater sedation and more amnesia in the midazolam group. Psychomotor performance, measured using the Trieger test, was equally impaired by either drug for up to two hours after sedation.¹⁷ Lee *et al.* compared topical lidocaine alone or with either midazolam titrated up to $70 \mu\text{g} \cdot \text{kg}^{-1}$ or diazepam up to $150 \mu\text{g} \cdot \text{kg}^{-1}$. Midazolam produced better (100%) amnesia and less retching than diazepam, with a similar clinical recovery time.⁴ Berggren reported that a bolus dose of midazolam $50 \mu\text{g} \cdot \text{kg}^{-1}$ was approximately equipotent to diazepam $150 \mu\text{g} \cdot \text{kg}^{-1}$. A higher proportion of subjects receiving midazolam reported amnesia for the procedure and fewer subjects who were undergoing endoscopy for the first time reported discomfort. Operating conditions and recovery of psychomotor performance did not differ between the two groups.¹⁸ Whenever comparing different studies or groups within studies the question of dose equivalence arises. Our protocol was designed to administer equivalent amounts of each benzodiazepine and narcotic. Whilst the dosage ratio of midazolam:diazepam (1:2) was in keeping with the early literature,^{3,19,20} subsequent studies^{18,21,22} have found that the equally sedative ratio is 1:3 or more.

Neither the present study nor any of the studies reviewed have shown a clear advantage in safety or more rapid recovery when midazolam is compared with diazepam. In two surveys^{11,12} of endoscopic practice, patient morbidity was reported equally frequently with either drug. In the context of the single small bolus dose generally used for upper GI endoscopy clinical recovery depends almost exclusively on drug redistribution rather than elimination. Compared with diazepam, midazolam redistribution half-life is only two to four times faster² and this may be insufficient to confer a clinically important advantage in recovery.

In this study we anticipated that hypoxaemia might be more common in subjects receiving midazolam/alfentanil because of a more rapid onset and a more profound peak effect. Because the established procedure using diazepam/meperidine did not routinely use oxygen supplements a study goal was to determine whether a change of practice was indicated. Lower minimum saturation and larger decreases during the procedure were found in older subjects irrespective of treatment group, but in each case were only transient. Bell *et al.* compared midazolam (mean dose 6.0 ± 2.8 mg) and diazepam (mean dose 11.5 ± 6.7 mg) in subjects whose mean age was 64.3 yr and found no differences between their effect on ventilation or mean lowest SpO_2 .²³ Gross *et al.* studied SpO_2 in subjects having colonoscopy with and without nasal oxygen sedated with variable doses of midazolam and meperidine. In their study minimum oxygen saturation among air breathers was related to dose of meperidine but not dose of midazolam. Others have shown that lower nadir saturations are associated with poor sedation,²⁴ increasing subject age,^{25,26} bolus injection as opposed to slow injection²⁵ and operator experience.²⁴

In conclusion, we found no reason to support the routine use of midazolam/alfentanil in the doses studied for sedation during upper GI endoscopy. The cost of treatment for a subject between 50–99 kg in our study was C\$3.20 for midazolam/alfentanil and C\$0.44 for diazepam/meperidine. The study results confirm that supplementation of inspired oxygen in otherwise healthy subjects given moderate amounts of sedation is not essential.²⁷ The question remains whether a lower dose of midazolam/alfentanil will produce acceptable conditions for the endoscopist and the patient with faster recovery.

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