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Bolus or slow titrated injection of midazolam prior to upper gastrointestinal endoscopy? Relative effect on oxygen saturation and prophylactic value of supplemental oxygen

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SUMMARY

A total of 131 patients undergoing upper gastrointestinal endoscopy were sedated with midazolam given as a bolus injection over 5 seconds. The oxygen saturation was continuously measured using a pulse oximeter. Supplemental oxygen was given via nasal cannulae at a rate of 3 litres per minute to 54 patients, while the remaining 77 patients only received oxygen if their oxygen saturation dropped below 85%. Both groups in the present series were compared with 3 previously published series of patients, in whom we had used intravenous midazolam as a slow titrated injection.

Despite using on average only two-thirds of the dose of midazolam, following bolus injection the degree of oxygen desaturation during the endoscopic procedure was greater, and the ability of supplemental oxygen delivered via nasal cannulae to prevent hypoxia was less ($P < 0.01$), than with a slow titrated injection.

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INTRODUCTION

At the present time approximately 90% of upper gastrointestinal endoscopies in the United Kingdom are performed under intravenous sedation with either diazepam or midazolam.[1] Endoscopy is, however, not without hazard and carries a mortality of the order of 1 in 10,000 examinations.[2–4] It has been estimated that about 50% of the morbidity and 60% of the mortality associated with the procedure relates to cardiopulmonary problems.[5,6] It has been repeatedly shown that patients may become hypoxic during upper gastrointestinal endoscopy as a result of drug-induced respiratory depression, and also the passage of the instrument itself which may cause a partial obstruction of the patient's upper airways.[5–7]

We have previously shown that when either diazepam or midazolam (which is at least twice as potent) are given in comparable dosage, the degree of oxygen desaturation occurring during endoscopy,[8] and the incidence of severe adverse outcomes,[1] are very similar. We have also shown that the hypoxia during upper gastrointestinal endoscopy can be largely prevented by pre-oxygenating the patient, and by giving supplemental oxygen via nasal cannulae during the precedure.[9]

In all our previous studies[8–12] it has been our practice to use a slow titrated dose of the benzodiazepine over 2–3 min. On the basis of our experience with this method of administering midazolam to a large number of patients, we have made recommendations regarding dosages in differing age groups.[12] However, these recommendations might not apply to the approximately one-third of endoscopists in the United Kingdom who use a rapid bolus injection method of administering a benzodiazepine.[1] Some endoscopists claim that they simply do not have time during a busy endoscopy list to employ a slow titrated dose method,[13] which they feel to be a less effective method of sedating the patient than a bolus injection. We had not previously detected an excess of deaths or serious adverse outcomes in the patients of those endoscopists employing a bolus injection method of sedation,[1] but we decided to see if there is any difference in the incidence of drug-related respiratory depression when compared with the slow titrated injection method. Furthermore, we wished to see if supplemental oxygen prevents serious hypoxaemia during endoscopy when a bolus injection technique is employed and, if so, whether the previously recommended oxygen delivery rate of 2 L/min[9] is adequate for such patients. Despite the re-assuring reports of the safety of bolus dose intravenous midazolam prior to endoscopy,[13] we decided to conduct our own preliminary study using significantly lower doses of midazolam and higher oxygen flow rates than we have used in any of our previously reported studies.[8–11]

PATIENTS, MATERIALS AND METHODS

A total of 131 patients undergoing upper gastrointestinal endoscopy were sedated with midazolam given as a bolus injection over less than 5 s. All patients were

weighed prior to endoscopy. No patient of any age was given greater than 5 mg midazolam. No patient over the age of 70 years received greater than 2.5 mg. All patients aged less than 60 years received 5 mg while the dose of those in the 60–70 age group was 2.5–5.0 mg at the discretion of the endoscopist (G.D.B.) Most of the over 70s received 2.5 mg but this dose was reduced to 1.5–2.0 mg for some of the most elderly patients. The oxygen saturation of all patients was measured continuously by a pulse oximeter with a pen recorder attached (Nelicor N-100 pulse oximeter). Supplemental oxygen was given via nasal cannulae at a rate of 3 L/min to 54 of the 131 patients. The remaining 77 patients only received oxygen if their oxygen saturation dropped below 85%.[14]

The mean pre-injection baseline oxygen saturation was determined from the traces of all 131 patients. The post-oxygen saturation was similarly determined in the 54 patients who were given supplemental oxygen. The time from the bolus ction of midazolam to the start of the intubation was estimated from the chart recordings of 50 patients—25 in each group. In all 131 patients, the *lowest* oxygen saturation recorded at any stage during the endoscopy was also estimated. If the oxygen saturation fell below 85% in the group of 77 not routinely receiving supplemental oxygen the rate of oxygen used was 4 L/min increasing, if necessary, to 10 L/min according to the response seen on the oximeter.[14]

Paired and unpaired *t*-tests and χ^2 tests were used to compare the different groups as and when appropriate.

RESULTS

Present series

Details of the 54 patients given supplemental oxygen, and the remaining 77 patients, are given in Table 1. The two groups were reasonably matched in terms of age, weight and dose of midazolam and baseline oxygen saturation. The mean ($\pm$s.d.) time from injecting the midazolam to the start of the endoscopy was similar in the two groups: 89.1 ($\pm$27.4) and 104.4 ($\pm$33.2) seconds, respectively ($P = 0.081$).

Following administration of supplemental oxygen at a rate of 3 L/min the oxygen saturation in this group of 54 patients rose significantly ($P < 0.001$) from 96.6 ($\pm$1.6)% to 99.3 ($\pm$0.9)%.

The mean oxygen saturation of both groups fell during the endoscopic procedure. Eleven patients in the no supplemental oxygen group had a fall of oxygen saturation to below 85% and were given nasal oxygen. In the 77 patients not given supplemental oxygen beforehand, the mean lowest oxygen saturation was 88.0 ($\pm$7.0)%, which is significantly less ($P < 0.001$) than the baseline saturation of 96.8 ($\pm$1.9)%. In contrast, although the supplemental oxygen groups oxygen saturation also fell significantly ($P < 0.01$) during the procedure from 99.3 ($\pm$0.9)% to 94.6 ($\pm$3.9)%, this drop was significantly less ($P < 0.001$) than occurred in the no supplemental oxygen group.

Table 1. Comparison between the two groups of patients given a bolus injection of midazolam prior to upper gastrointestinal endoscopy. Effect of supplemental oxygen via nasal cannulae at a rate of 3 litres per minute

	No supplemental oxygen	Supplemental oxygen
Number	77	54
Sex ratio (M/F)	39/38	32/22
Weight–mean (s.d.)	67.4 (13.2) kg	68.8 (15.2) kg
Age		
Mean (s.d.)	56.3 (16.5) year	57.7 (18.7) year
Range	22–85 year	21–89 year
% > 70 year	19/58 = 32.8%	16/38 = 42.1%
Weight	67.4 (13.2)	68.8 (15.2)
Dose of midazolam		
Mean (s.d.)	4.2 (1.3)	4.1 (1.2)
Range	1.5–5.0 mg	1.5–5.0 mg
Mean mg/kg body wt	0.065 (0.022)	0.061 (0.019)
Range mg/kg body wt	0.023–0.116	0.026–0.109
Time of injection to intubation:		
Mean (s.d.)	104.4 (33.2) s	89.1 (27.4) s
Range	62–218 s	45–186 s
Baseline O_2 saturation		
Mean (s.d.)	96.8 (1.9)	96.6 (1.6)
Range	92–100	93–100
Post O_2 saturation		
Mean (s.d.)	—	99.3 (0.9)
Procedure lowest O_2 saturation		
Mean (s.d.)	88.0 (7.0)	94.6 (3.9)

Supplemental oxygen increased oxygen saturation significantly ($P < 0.001$) and the fall in oxygen saturation during upper gastrointestinal endoscopy was much less ($P < 0.001$) than in the group not given supplemental oxygen.

It was possible to divide the 77 patients who were not given supplemental oxygen into four different age groups, and then compare the mean fall of oxygen saturation during the procedure. The results are shown in Table 2. In the over 70 years of age group, the mean fall of oxygen saturation of $10.4 \pm 8.2\%$ was greater than in the 60–70 year age group ($7.9 \pm 4.7\%$), despite the mean dose of midazolam used to sedate the patient being less than half that used in the younger group (2.3 ± 0.3 mg *vs* 4.7 ± 0.9 mg, $P < 0.001$). All patients under the age of 60 years received 5 mg of intravenous midazolam as a bolus injection, but the patients under the age of 40 had significantly smaller falls in oxygen saturation than those in the 40–60 age group (5.8 ± 4.5 *v* $10.2 \pm 6.4\%$, $P = 0.026$).

For purposes of comparison, in Table 3, we have compared the present series of 77 patients undergoing upper gastrointestinal endoscopy who were sedated with a bolus injection of midazolam with the two previously published series of 100 patients[10] and 51 patients[8] in which the midazolam was administered as a slow

Table 2. Fall in percentage oxygen saturation during endoscopy following sedation with a bolus injection of midazolam—the effect of age

Group	Mean	s.d.	*n*
Age > 70 years:			
Age	76.8	4.0	19
Dose	2.3	0.3	19
mg/kg	0.037	0.008	19
fall O_2 (%)	10.4	8.2	19
Age 60–70 years:			
Age	63.8	3.2	19
Dose	4.7	0.9	19
mg/kg.	0.067	0.017	19
fall O_2 (%)	7.9	4.7	19
Age 40–60 years:			
Age	49.8	5.7	24
Dose	5.0	0.0	24
mg/kg.	0.074	0.015	24
fall O_2 (%)	10.2	6.4	24
Age 20–40 years:			
Age	31.4	5.1	15
Dose	5.0	0.0	15
mg/kg	0.082	0.017	15
fall O_2 (%)	5.8	4.5	15

The mean percentage fall of O_2 in the 20–40s compared with the 40–60s (5.8 *vs* 10.2%), is significant ($t = 2.529$, DF 37, $P = 0.026$).

Table 3. A comparison between the present series of 77 patients undergoing endoscopy, who were sedated with a bolus injection injection of midazolam, and 2 previously published series of 100 patients[10] and 51 patients[8] in which the midazolam was administered as a slow titrated injection

	Present series (n) = 77)	Previous series[10] (n = 100)	Previous series[8] (n = 51)
Sex (M/F)	39/38	52/48	24/27
Mean age (years)	56.3 (16.5)	62.4 (15.0)	65.8 (11.5)
Dose of midazolam (mg)	4.2 (1.3)	6.3 (2.8)*	6.0 (2.8)*
Time from injection to intubation (seconds)	104.4 (33.2)	228 (72)*	204 (55)*
Baseline O_2 saturation (%)	96.8 (1.9)	95.4 (1.8) N.S.	94.9 (2.0) N.S.
During endoscopy O_2 (%)	88.0 (7.0)	89.0 (7.7) N.S.	88.5 (4.7) N.S.

S.d. given in parentheses.
* = $P < 0.001$, compared with present series.

Table 4. Comparison between the present series of 54 patients (bolus injection) and previous series of 50 patients (slow titrated injection)[9] both of which received supplemental oxygen via nasal cannulae

	Present series ($n = 54$)	Previous series[9] ($n = 50$)
Sex (M/F)	32/22	29/21
Mean age (years)	56.7 (18.7)	58.0 (15.2)
Dose of midazolam (mg)	4.1 (1.2)	6.7 (3.0)***
Time from injection to intubation (seconds)	89.1 (27.4)	246 (66)***
Rate of nasal oxygen	3 L/min	2 L/min
Baseline O_2 saturation (%)	96.6 (1.6)	95.7 (1.8) N.S.
Post supplemental O_2 (%)	99.3 (0.9)	97.9 (1.4)**
During endoscopy O_2 (%)	94.6 (3.9)	96.3 (3.8)*

S.d. given in parentheses.
* = $P < 0.05$, ** = $P < 0.01$ and *** = $P < 0.001$, compared with present series.

titrated injection. In Table 4 we compare the present series of 54 patients (bolus injection) and a previous series of 50 patients (slow titrated injection),[9] both of whom received supplemental oxygen via nasal cannulae.

DISCUSSION

In a postal survey[1] sent out to over one thousand endoscopists in the United Kingdom, it was found that approximately one third was using a bolus injection of a benzodiazepine rather than the more generally recommended slow titrated method to sedate their patients prior to endoscopy.[1] Higher blood levels of midazolam are likely to be achieved following a rapid bolus injection, as used in our present study, rather than when the drug is given as a titrated slow injection over several minutes,[15] as used in all our previous studies.[8–11] Midazolam is highly protein-bound (94–98%) as, indeed, is diazepam (97–99%). Thus, one could postulate that following a bolus injection of either compound, the percentage of the drug in the free unbound form which would be available to occupy benzodiazepine receptor sites would also be greater.[15] The theoretical advantage of a rapid bolus injection of a benzodiazepine is that its speed of onset would be quicker and the endoscopist able to start the procedure with the patient adequately sedated earlier than if he employed the slow titrated injection technique. Furthermore, the patient would require a smaller dose of the sedative, with benefits in terms of a more rapid recovery and reduced drug cost.

The theoretical disadvantage of the bolus injection method of sedating endoscopy patients is the increased risk of drug-induced respiratory depression, which would be even greater if the benzodiazepine were to be given in conjunction with an opiate.[1,15]

Table 5. Comparison between the present series of 77 patients sedated by bolus injection technique and previous series of 100 patients[10] sedated by slow titrated dose method—relative effect on lowest oxygen saturation level achieved during endoscopy

	> 90%	85–90%	80–85%	< 80%
Bolus	36	26	9	6
Titrated	69	20	7	4

χ^2 test 8.967, $P < 0.05$.

The present study has confirmed[13] that adequate sedation prior to endoscopy can be achieved with less than two-thirds of the dose required when a slow titrated injection method is used. Furthermore, we were able to start intubating the patient after about 1.5 min, compared with about 4 min when the titrated method was used (please see Tables 3 and 4). If performing busy endoscopy list of 10–15 cases per list, this could make over half an hours difference to the length of the list. By drawing up the midazolam into syringes containing either 5 or 2.5 mg quantities, depending on the patients age, it is possible for a single 10 mg ampoule of the drug, (5 ml) to be used to sedate between 2 and 4 patients with consequent savings in terms of drug costs.

Although not formally tested in the present study, it is our impression that the degree of sedation and antegrade amnesia, during the bolus injection, was similar to that with the titrated technique in which the dose of sedation was greater.

The present study has also confirmed the value of supplemental oxygen[9] in reducing and, in many cases, preventing significant hypoxaemia during endoscopy. Despite using 3 litres of oxygen per minute via the nasal cannulae, in the present study this was less successful in preventing oxygen desaturation during the gastroscopy than had been 2 L/min in the previous titrated dose study[9] (please see Table 4).

As can be seen from Table 3, despite the much smaller doses of midazolam used in the present bolus group, compared with either of the comparable titrated dose groups, the fall in oxygen saturation was greater. In the case of the series of 100 patients[10] the mean lowest oxygen saturation of $89.0 \pm 7.7\%$ was only slightly greater than the bolus series but 11 of the bolus and none of the titrated series received oxygen. As can be seen from Table 5, when the two sets of patients were divided up into four groups (greater than 90% saturation, 85–90%, 80–85% and less than 80%) the lowest falls in oxygen saturation during endoscopy were significantly greater in the present bolus injection series (χ^2 test 8.967, $P < 0.05$). Furthermore, in the other previously reported series where a slow titrated injection was used[8] (see Table 3), the mean fall in oxygen saturation of $6.4 \pm 3.7\%$ was significantly less, ($P < 0.02$) than the present bolus injection group, ($8.8 \pm 6.4\%$).

The comparison with the present and previous study underlines the fact that if endoscopists are to use a bolus injection technique to sedate their patients they

must use a much smaller dose of benzodiazepine than their colleagues employing the slow titrated injection method and also be prepared to more readily use supplemental oxygen at higher flow rates.

As shown in Table 2, the elderly are particularly vulnerable to drug-induced respiratory depression when a bolus injection is used. The dose of midazolam we previously recommended for use in the over 70's when a titrated dose regime[12] was used will need to be considerably reduced if a bolus technique is employed. Further studies are required to more accurately define safe dose regimes and the optimum method and rate of administering supplemental oxygen if we are to further reduce the cardio-pulmonary complications of endoscopy which still account for some 60% of the mortalities associated with the procedure.[2–6]

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