Intravenous midazolam: A study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy

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- 1 Intravenous midazolam (mean dose of 6.3 mg) was given to 100 consecutive patients coming to endoscopy.
- 2 All patients had an ear oximeter attached throughout the procedure to record continuously their levels of oxygen saturation.
- 3 Eighty-five of the 100 patients had pre-endoscopy respiratory function tests measured, and 82 wore an induction plethysmograph vest to get a continuous qualitative estimate of respiratory rate and excursion throughout the procedure.
- 4 Following intravenous midazolam a reduction in respiratory excursion was observed in 80% of patients.
- 5 The initial baseline oxygen saturation of 95.4% fell 3.3% ($P < 0.0005$) following intravenous midazolam to 92.1%.
- 6 During the endoscopic procedure there was a further 3.1% decrease in oxygen saturation to 89.0% ($P < 0.0005$) and in 7% the level fell to below 80%.
- 7 Age, sex, dose of midazolam given and pre-endoscopy respiratory function tests failed to identify those patients at risk of hypoxia during the endoscopy.

Keywords intravenous midazolam endoscopy oxygen desaturation

Introduction

In many endoscopy units midazolam appears to be replacing diazepam as the intravenous sedative of choice (Dundee *et al.*, 1984). Its supposed advantages over diazepam include a shorter half-life and lack of venous irritation, pain and phlebitis. There have been at least eight previous studies (for references see below) in which oxygen saturation has been measured when upper GI endoscopy was performed under intravenous diazepam sedation. Surprisingly, there appeared to be no such similar study using intravenous midazolam, despite reports of respiratory depression and occasional deaths, especially in

elderly patients given the drug for endoscopy (CSM Current Problems 14th July, 1985).

We have therefore studied changes in oxygen saturation with midazolam sedation before and during endoscopy and related the changes to ventilatory function to 100 patients.

Methods

We studied 100 consecutive patients attending for endoscopy on the one day of the week when a respiratory physiology technician was available.

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The following measurements were performed:

(a) in all 100 patients oxygen saturation was continuously recorded using an ear oximeter (Hewlett Packard Co 4720 1A SANTAGO, California)

(b) in 82 patients a GVT induction plethysmograph (P. K. Morgan Limited, Chatham, Kent) was used to record simultaneously depth and rate of respiration. The instrument operates by detecting the change in inductance in a coil wound into a vest worn by the patient. No attempt was made to calibrate the induction plethysmograph against the patient lung volumes so consequently any observed change in respiratory excursion was of a qualitative rather than a quantitative nature.

(c) in 85 patients ventilatory function as assessed by FEV₁ and FVC was measured before endoscopy and recorded as a percentage of the predicted value for that patient's age and sex.

Informed consent was obtained from all patients.

A lignocaine throat spray (4%) was given to anaesthetize the back of the throat. After an adequate 'baseline' recording of the patient's oxygen saturation had been obtained using the ear oximeter and, in 82 patients, a baseline recording of respiratory rate and excursion with the induction plethysmograph the injection of midazolam was commenced. In most patients, approximately 2.5 mg of midazolam was administered intravenously over 30 s, while elderly patients received only 1 mg of the drug. If, after 1 to 2 min, adequate sedation had not been achieved, further small increments of midazolam were given until the appropriate level of consciousness was reached (i.e. drowsy, but able to swallow on command).

The intubation itself was not commenced until any observed fall in oxygen saturation following intravenous midazolam had stabilised and a new baseline had been obtained. The time from the start of the injection of midazolam to the intubation of the patient was recorded. The *lowest*

oxygen saturation obtained during this period of study was noted. All intubation of the upper oesophagus was done under direct vision by one of us (GDB) and the oesophagus, stomach and duodenum examined in the standard way. Again, the *lowest* oxygen saturation obtained at any time between the insertion and removal of the gastroscope was recorded. The presence of gagging or choking/coughing was noted. The relatively large diameter Olympus GIFIT endoscope was used in 97 subjects, while in three subjects, with oesophageal strictures undergoing oesophageal dilatation, the much smaller Pentax FG 28A was used.

Statistics

Conventional statistical methods have been used. Paired *t*-tests and Wilcoxon's rank sum tests have been used to determine the significance of changes in oxygen saturation. Linear regression has been used to examine the correlation of changes in oxygen saturation with other variables, where quoted *r* refers to Pearson's correlation coefficient.

Results

Table 1 shows the mean age and the mean dose of midazolam given, which was similar in men and women. Their ventilatory function tests are summarised in Table 2.

The mean percentage oxygen saturation before injecting midazolam was 95.4% $\pm$ 2.2% (range 86 to 99). The mean time from the start of the midazolam injection to the beginning of the intubation was 3 min 42 s (range 1 min 40 s to 8 min 40 s).

Following intravenous midazolam, there was 3.3% fall in oxygen saturation ($P < 0.0005$, $t = 9.66$ on paired *t*-testing). The *lowest* oxygen saturation recorded ranged from 73 to 98%—

Table 1 Mean age of patients and dose of midazolam used to achieve sedation ($n = 100$)

	Males	Females	Total
Number of cases	52	48	100
Mean age (years)	62.7	62.1	62.4
s.d.	± 13.7	± 16.6	± 15
range	21–85	16–89	16–89
Dose of midazolam (mg)	6.0	6.5	6.3
s.d.	± 2.7	± 3.0	± 2.8
range	1.0–15.0	2.5–15.0	1–15

Table 2 Respiratory function tests of patients ($n = 85$) prior to endoscopy

	Males	Females	Total
FEV ₁ /FVC*	74%	80%	77%
s.d.	±10	±11	±11
range	51–98	57–100	51–100%
FEV ₁ *	90%	90	90%
s.d.	±23	±29	±26
range	47–152%	36–155%	36–155%
FVC*	96%	90%	93%
s.d.	±20	±26	±23
range	53–151%	32–141%	32–151%

*As percentage predicted for age and sex

mean $92.1 \pm 4.2\%$. The percentage desaturation was similar in men and women (Table 3).

The induction plethysmograph traces of all 82 patients were carefully examined for any qualitative changes occurring after intravenous midazolam. One trace was not of sufficient quality to comment, leaving 81 traces for analysis. Respiratory excursion was clearly depressed in 65 (80%) and unchanged in the remainder. As can be seen from Figure 1 periods of hypoventilation following intravenous midazolam were frequently associated with a fall in O₂ saturation. In most cases, respiratory rate was unaltered unless (as in Figure 1) cyclical periods of frank apnoea occurred.

A further small, but significant ($P < 0.0005$, $t = 4.55$ paired t -test) fall (mean 3.1%) in oxygen saturation occurred during endoscopy. The mean lowest oxygen saturation observed during endoscopy was $89.0 \pm 7.7\%$ (range 51 to 98.5%) Again, there were no important differences discernible between male and female patients (Table 3).

In 54 of the 100 patients, no appreciable period of coughing, gagging or choking occurred at any

time during the endoscopy. In the remaining 46 patients, periods of gagging or coughing lasting more than a few seconds were recorded, usually during intubation or when the endoscope was turned into a 'J loop' to examine the fundus and cardia of the stomach. In 25 (55%) this produced a temporary fall in oxygen saturation (Figure 2); 14 (30%) were unaltered, while in 7 (15%) the oxygen saturation appeared to rise at the time of coughing/gagging.

The marked falls in oxygen saturation were unpredictable and could not be related to the following variables: (a) age or sex of the patient ($r = 0.03$); (b) previous measurements of ventilatory function (the r values for FEV₁/FVC ratio, FEV₁ and FVC (all expressed as percentages of predicted) (being -0.03 , -0.07 and -0.06 respectively); (c) the dose of midazolam used ($r = -0.06$); (d) the initial oxygen saturation ($r = -0.09$).

Discussion

In the present study, we have clearly shown that small doses of intravenous midazolam (mean dose 6.3 mg), even when administered cautiously over several minutes, can produce a small but statistically significant fall in oxygen saturation, even before the endoscope is passed. In most cases, this fall is modest and unlikely to be of clinical significance, although in two of a 100 subjects in our series, the level fell to 73% (Table 4). The cause of the hypoxaemia is likely to relate to the central depressant effect of the drug producing hypoventilation since the induction plethysmograph trace showed a fall in respiratory excursion in approximately 80% of our patients.

In support of this hypothesis Morel *et al.* (1984) have recently shown that intravenous midazolam (0.1 mg kg^{-1} given over 30 s) produced a significant decrease in mean respiratory flow resulting

Table 3 Mean lowest oxygen saturation (%) obtained in the 100 endoscopy patients before and after intravenous midazolam and during the endoscopy procedure

	Males	Females	Total
Baseline saturation	95.3	95.5	95.4
s.d.	± 2.1	± 2.3	± 2.2
range	90–99	86–98.5	86–99
Post-injection saturation	92.6	91.6	92.1
s.d.	± 2.9	± 5.3	± 4.2
range	85–98	73–98	73–98
During endoscopy saturation	88.9	89.1	89.0
s.d.	± 8.1	± 7.3	± 7.7
range	51–97	59–98.5	51–98.5

Figure 1 Oxygen saturation and chest movements continuously recorded using an ear oximeter and induction plethysmograph respectively. Following intravenous midazolam, the oxygen saturation falls slightly from 97% to a minimum of 86% and starts to rise again so that at the time of intubation, the saturation is again over 90%. The respiratory rate, and particularly depth of respiration is initially reduced following intravenous midazolam and as a consequence the oxygen saturation falls. This patient, like several others, showed a cyclical respiratory pattern reminiscent of Cheyne-Stokes breathing.

Figure 2 Oxygen saturation and chest wall movements continuously monitored throughout the gastroscopy using an ear oximeter and induction plethysmograph. Following intravenous midazolam, the baseline O_2 saturation fell from 97% to a minimum of 87% and then began to slowly rise again. As in Figure 1, the respiratory rate, and particularly respiratory excursion, was reduced by the intravenous sedative and as a consequence O_2 saturation fell. Following intubation the patient started gagging and coughing and the O_2 saturation fell alarmingly to a low point of only 51%. The oxygen saturation quickly rose again once the patient's coughing stopped so that shortly after removing the gastroscope, the O_2 saturation was again over 90%.

Table 4 Numbers of patients with significant oxygen desaturation before and after intravenous midazolam and during endoscopy

Oxygen saturation	Baseline	Post-injection	During endoscopy
85–90%	1	16	20
80–85%	0	2	7
70–80%	0	2	3
60–70%	0	0	1
>60%	0	0	3

in a 39% reduction in tidal volume (V_T). Larger doses of midazolam used for induction of anaesthesia (0.15 – 0.3 mg kg^{-1}) increase PaCO_2 (Reves *et al.*, 1978; Reinhardt *et al.*, 1983) but are said not to usually influence PaO_2 (Crawford *et al.*, 1984; Reves *et al.*, 1979). However, in a recent extensive review of midazolam (Dundee *et al.*, 1984) mention is made of the fact that a decrease in PaO_2 has been reported with doses of 0.15 to 0.2 mg kg^{-1} (Forster *et al.*, 1983; Reinhart *et al.*, 1983).

To our knowledge, there has been no previous study of the effects of midazolam on oxygen saturation before or during endoscopy. In contrast, there have been at least eight studies of the effect of diazepam on arterial oxygen tension during endoscopy. Three of these studies have, as in the present study, used an ear oximeter (Atluri & Ravry, 1978; Rostykus *et al.*, 1980; Lieberman *et al.*, 1985) while the other five have relied on multiple arterial punctures (Whorwell *et al.*, 1976; Ona & Israel, 1981; Rozen *et al.*, 1982; Pecora *et al.*, 1984).

The effect of diazepam on oxygen saturation in these eight studies has been variable, but what seems clear is that there is a consistent fall in oxygen tension following endoscopic intubation. This fall in O_2 tension occurs even when no intravenous diazepam is used (Whorwell *et al.*, 1976; Rostykus *et al.*, 1980; Lieberman *et al.*, 1985), but is more marked and protracted if intravenous diazepam had been given first (Lieberman *et al.*, 1985) particularly if combined with other premedication (Atluri & Ravry, 1978; Rozen *et al.*, 1982) or a large diameter endoscope is employed (Lieberman *et al.*, 1985; Rozen *et al.*, 1981, 1982).

In our own study, using midazolam, the further significant fall in oxygen saturation following intubation with the gastroscope, is presumably a

combination of the hypoventilation produced by midazolam, plus the mechanical effect of the instrument partly occluding the patient's upper airways.

It was of considerable concern to us that 7% of our patients desaturated to below 80% during the endoscopic procedure (Table 4), since cardiac arrhythmias are particularly liable to occur at times of hypoxaemia (Rostykus *et al.*, 1980). Several groups have tried to identify which patients are at particular risk of marked desaturation. Like Whorwell *et al.* (1978) we did not find pre-endoscopy respiratory function tests useful, but in both studies few patients had an FEV_1/FVC ratio of less than 60%—a level below which others (Rostykus *et al.*, 1980; Lieberman *et al.*, 1985) have found these tests to be of predictive value.

It was of interest that three of our five patients who showed the greatest desaturation had large hiatus hernias associated with free gastro-oesophageal reflex. Aspiration of gastric contents into the lungs is known to occur during endoscopy (Taylor *et al.*, 1972; Prout & Metreveli, 1972). In these cases the fall in oxygen tension might be expected to occur in part as a result of aspiration and atelectasis affecting regional ventilation (Ona & Israel, 1981). In addition, we were impressed by the close temporal relationship between the onset of gagging, coughing/choking and a fall in oxygen saturation. It would be tempting to administer further intravenous sedation to such patients, thereby still further depressing ventilation, with potentially disastrous consequences.

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