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Speed of reversal of midazolam-induced respiratory depression by flumazenil – a study in patients undergoing upper G.I. endoscopy

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Intravenous midazolam was given to 17 patients coming to upper G.I. endoscopy. All patients had an ear oximeter and calibrated induction plethysmograph attached to record oxygen saturation and minute volume continuously. Midazolam induced significant depression of respiration. Following removal of the endoscope, a new base line was obtained before giving intravenous flumazenil in an attempt to reverse the sedative and ventilatory effects of midazolam. When 0.5 mg of flumazenil was given over 20 s, followed by 0.1 mg every minute, up to a total of 1.0 mg, all patients were apparently awake in under 2 min. Although the flumazenil had clearly reversed the sedative effects of midazolam, the ventilatory effects were largely uninfluenced. The implications are discussed.

Key words: Gastroscopy; reversal with flumazenil; sedative; ventilatory effect of midazolam.

Many studies have now shown that intravenous diazepam (1–9) and midazolam (10–12) in the doses used for sedation prior to O.G.D. (oesophago-gastro-duodenoscopy) can cause significant hypoxaemia. Even without intravenous benzodiazepine sedation, some fall in oxygen saturation is observed during O.G.D. (1, 5, 7, 9), presumably as a result of the endoscope partially occluding the patient's upper airway. The fall in oxygen saturation at the time of O.G.D. can be limited by: a) keeping the dose of benzodiazepine to a minimum (1, 5, 7, 9); b) avoiding simultaneous use of narcotics, such as pethidine and alfentenil (7); c) using a small diameter endoscope (7, 9); and d) having the procedure performed by an experienced endoscopist (13).

Prevention of hypoxaemia at the time of O.G.D. is not purely of academic interest since about 60% of the deaths following O.G.D. are cardio-pulmonary in type (14–19) and thus ought in many instances to be largely preventable. Whereas, anaesthetic related deaths have dropped dramatically in the last 20 years as a result of better training of anaesthetists, and the wider availability of safety and monitoring procedures etc. (20), mortality following O.G.D. remains between 1 in 5000 and 1 in 10 000 (21). Most cardiac arrhythmias during fibre optic gastroscopy (2, 9, 22, 23) or bronchoscopy (24–26) are observed to occur at the time of hypoxia. Although hypoxia during O.G.D. can largely be prevented by using supplemental oxygen delivered by nasal cannulae (27), in practice very few endoscopists in the United Kingdom use supplemental oxygen (21).

Our concern was that the introduction in the United Kingdom of flumazenil, the first specific benzodiazepine antagonist, might paradoxically increase rather than decrease endoscopically-related deaths and the frequency of major adverse events. We felt that some endoscopists might largely ignore the possibility of respiratory/cardio-vascular problems occurring with intravenous benzodiazepines because they believed they had an effective antagonist available if problems arose. It has been shown repeatedly that clinical observation is totally inadequate to detect the early warning signs of respiratory depression and hypoxia (28). Therefore, we used a combination of an ear oximeter and calibrated induction plethysmograph vest to study the speed of reversal by flumazenil of midazolam-induced respiratory depression following O.G.D. Our results suggest that, although flumazenil rapidly and effectively reversed the sedative effects of midazolam, its effect on benzodiazepine-induced respiratory depression was far from impressive.

PATIENTS AND METHODS

In all, we studied 17 patients before, during and after O.G.D. The method used has been described in detail elsewhere (11), but briefly: a) In all patients oxygen saturation was continuously recorded using an ear oximeter (Hewlett Packard Co. 47201A, Santiago, California). b) In all patients a G.V.T. induction plethysmograph (P. K. Morgan Ltd., Chatham, Kent) was used to record simultaneously depth and

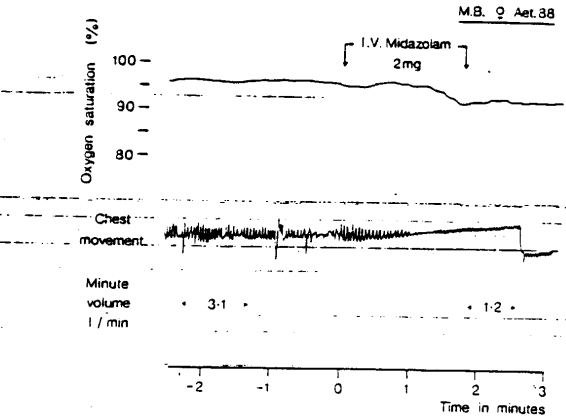

Fig. 1. Oxygen saturation and chest movements continuously recorded using an ear oximeter and induction plethysmograph respectively. Following a titrated dose of intravenous midazolam (2.0 mg) M.B.'s respiratory excursion was reduced from an estimated 3.1 l·min^{-1} to 1.2 l·min^{-1}, two and a half min after the start of injection. The oxygen saturation dropped only slightly from 96% to 93%.

rate of respiration. The instrument operates by detecting the change in inductance of a coil wound into the vest worn by the patient. c) In all patients the induction plethysmograph deflections were calibrated against volume measurement made at the mouth using a pneumotachograph and integrator (Si-Plan Electronics), so that a value was obtained for minute ventilation at each stage in the procedure. Unfortunately three of the 17 patients were unable to co-

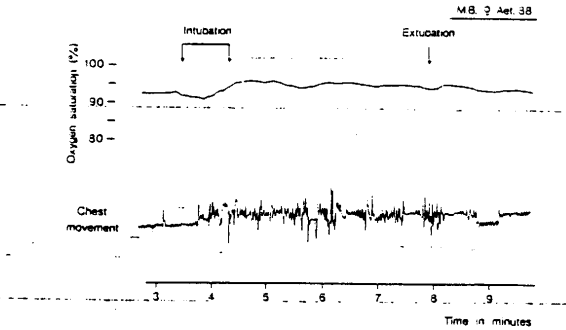

Fig. 2. A continuation of Fig. 1. Following intubation there was a marked change in the recorded chest movements. This is thought to represent the patient's respiratory efforts against a partly occluded upper airway as a result of the presence of the endoscope. This type of trace is reminiscent of that obtained using similar equipment to study sleep apnoea. Following removal of the endoscope, the respiratory pattern began to return to pre-intubation form. This patient's oxygen saturation remained reasonably satisfactory throughout the endoscopic procedure.

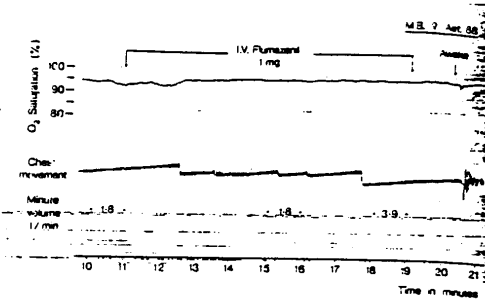

Fig. 3. A continuation of Fig. 1 and 2. Following removal of the endoscope, a new post-endoscopy (pre-flumazenil) base line was obtained, the estimated minute volume being 1.8 l·min^{-1} which was still significantly less than the pre-midazolam base line (Fig. 1) of 3.1 l·min^{-1}. Following intravenous flumazenil the patient's minute volume gradually rose to its pre-midazolam level over a period of approximately 8 min.

operate fully with the calibration of their plethysmograph vest and were excluded from further analysis.

Informed consent was obtained from all patients and the study was approved by the ethics committee of the Ipswich Hospital.

A lignocaine throat spray (4%) was given to anaesthetise the back of the throat. A steady "base line" recording of the patient's oxygen saturation was then obtained using the ear oximeter. The induction plethysmograph was calibrated using the pneumotachograph and hence a "base line" value of the patient's minute volume (litres per minute) was estimated.

The patients were sedated with intravenous midazolam using the dose regime previously described (10, 11). The time over which the drug was administered was marked on the paper recording following the intravenous midazolam; intubation was not attempted until any fall in oxygen saturation and ventilation had stabilised and a new

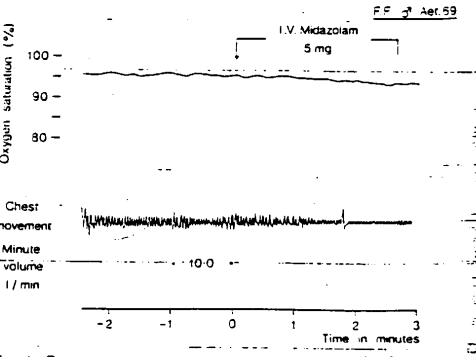

Fig. 4. Oxygen saturation and chest movements continuously recorded using ear oximeter and induction plethysmograph respectively. As in Fig. 1, following intravenous midazolam (5.0 mg in this example), the patient's depth and rate of respiration were markedly reduced. The associated fall in oxygen saturation was very modest from 96% to 92.5% just prior to intubation.

Table 1

Mean ± s.d. and individual mean volume ($l \cdot min^{-1}$) results in 13 patients before B) and after intravenous midazolam (PM). Also minute volumes following removal of the endoscope, i.e. before flumazenil (BF) and then 1 min after administering 0.5 mg of intravenous flumazenil (F.0.5 mg). Further minute volume measurements were made every minute, as further flumazenil was administered at 0.1 $mg \cdot min^{-1}$ up to a total of 1.0 mg (F.0.6–F.1.0). A final measurement of minute volume was then made 1 min later (Final). Unfortunately the data on subjects nos. 6 and 7 are incomplete because of failure of the pen recorder at the time intervals shown with an asterisk.

Subject	B	PM	BF	F.0.5 mg	F.0.6 mg	F.0.7 mg	F.0.8 mg	F.0.9 mg	F.1.0 mg	Final
1	8.10	5.00	6.40	6.80	6.50	8.90	6.00	6.50	7.50	7.80
2	4.80	2.80	3.20	2.90	3.30	3.70	3.60	2.70	3.70	3.70
3	4.60	2.80	3.10	4.00	3.10	2.10	2.40	3.00	2.70	2.60
4	4.80	3.40	4.90	3.70	4.80	3.60	4.70	4.90	4.30	4.00
5	9.30	4.60	4.60	5.10	4.90	5.20	4.40	5.40	5.30	8.60
6	5.80	4.10	4.60	5.60	*	*	*	*	*	4.40
7	4.50	2.20	2.00	1.70	2.00	2.50	2.20	*	2.40	3.00
8	4.50	2.80	5.70	4.70	5.60	4.00	4.20	3.70	4.00	4.20
9	7.60	6.80	5.00	6.20	5.70	4.80	3.90	4.00	3.80	5.00
10	8.70	6.60	6.50	7.00	6.80	5.30	5.10	9.20	6.10	5.00
11	15.10	6.00	5.90	6.00	5.40	9.00	7.00	6.30	6.40	9.30
12	8.70	7.80	7.50	6.90	11.90	10.20	8.50	7.50	6.10	5.30
13	4.40	3.40	3.40	3.40	4.20	3.90	4.20	4.20	4.10	4.70
Mean	6.99	4.48	4.83	4.92	5.35	5.27	4.68	5.22	4.70	5.20
s.d.	3.09	1.82	1.58	1.69	2.50	2.66	1.80	2.00	1.57	2.09

* Trace unsatisfactory for estimation of minute volume because of failure of pen recorder.

base line was obtained. The time from the start of the injection of the sedative to intubation of the patient was recorded. The lowest oxygen saturation obtained during this period (i.e. the "post injection oxygen saturation") was noted. The minute volume over the 20–30 s prior to intubation (i.e. the "post injection minute volume") was calculated from the already calibrated induction plethysmograph recording.

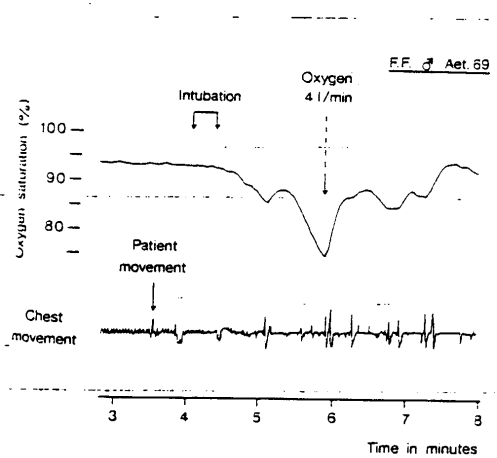

Fig. 3. A continuation of Fig. 4. Following passage of the endoscope, the patient's oxygen saturation was seen to drop alarmingly to less than 75%, presumably as a result of a) hypoventilation and b) partial obstruction of the upper airways by the endoscope. Following administration of supplemental oxygen via nasal cannulae at a rate of 4 $l \cdot min^{-1}$, the patient's oxygen level rapidly rose to over 90% in less than 2 min.

All intubations of the upper oesophagus were carried out under direct vision by one of us (G.D.B.), and the oesophagus, stomach and duodenum were examined in the usual way. Again, the lowest oxygen saturation obtained at any time between the insertion and removal of the gastroscope was recorded. The relatively large diameter Pentax 3¼ F.G.A. endoscope was used in all patients. Minute volume was not measured during endoscopy because any tendency to cough or choke made measurement difficult, and because the presence of the endoscope in the upper airways invalidated the relationship established between changes of ventilation and plethysmography.

Once the patient's breathing had settled down following removal of the endoscope, we estimated the patient's minute volume from the tracing – the post-endoscopy minute volume. Fig. 1, 2 and 3 show a typical trace. Following measurement of the new post-endoscopy (i.e. before flumazenil) base line, intravenous flumazenil was administered. In the first patient flumazenil was given as 0.2 mg over 20 s and then a further 0.1 mg every 1 min until a total of 1.0 mg had been administered. A further 13 patients received 0.5 mg of flumazenil over 20 s, followed by 0.1 mg every 1 min up to a total of 1.0 mg. One patient (F.F.) had a double study. In each case, the time it took the patient to wake up after receiving flumazenil was recorded on the chart.

RESULTS

The results in the first patient, an 88-year-old lady, given 2.0 mg of intravenous midazolam and later reversed using flumazenil, are shown in Fig. 1–3. The mean age of the 13 patients given 0.5 mg of flumazenil followed by 0.1 mg at 1-min intervals, was 63 years (range 31–80 years). There were seven female and six male patients. The mean ± s.d. dose of intravenous midazolam was 6.1 ± 2.2 mg (range 3–10 mg). On a $mg \cdot kg^{-1}$ body weight basis, this was 0.1 ± 0.03 $mg \cdot kg^{-1}$ (range 0.06–0.17 $mg \cdot kg^{-1}$). As can be seen from Table 1, the mean minute volume of 6.99 ± 3.09

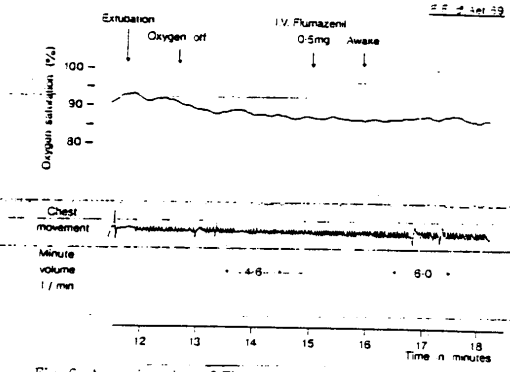

Fig. 6. A continuation of Fig. 4 and 5. Following removal of the gastroscope, a new post-endoscopy (pre-flumazenil) base line of 4.6 l was obtained (i.e. still less than half the pre-midazolam base line – see Fig. 4). Following discontinuation of the supplemental oxygen, the oxygen saturation again fell to 86%. Within 1 min of giving 0.5 mg of flumazenil, the patient was awake. However, his respiratory rate and excursion increased much more slowly. In contrast to the rapid effect of supplemental oxygen on oxygen saturation seen in Fig. 5, the patient's oxygen saturation remained below 90% for several minutes following intravenous flumazenil, despite his being apparently wide awake.

$l \cdot min^{-1}$ fell significantly ($P = 0.002$) following intravenous midazolam to $4.48 \pm 1.82\ l \cdot min^{-1}$ prior to the gastroscopy. Following removal of the gastroscope and re-establishment of a post-endoscopy (before flumazenil) base line, the minute volume was still significantly depressed ($P = 0.01$) at $4.83 \pm 1.58\ l \cdot min^{-1}$. Following the 0.5 mg of flumazenil, all patients woke up rapidly (mean 1.1 min, range 0.5–1.8 min), but the minute volume did not change significantly over the next 6 min (Table 1, Fig. 7).

The 13 patients' oxygen saturation data are shown in Table 2 and Fig. 7. There was a small drop ($P = 0.08$) in oxygen saturation from a base line level of $94.7\% \pm 2.3$ to $93.2\% \pm 3.1$. In only one patient (Fig. 4–6) did the oxygen level fall to potentially dangerous levels during the endoscopic procedure. No other patient required supplemental oxygen.

Flumazenil had little effect on oxygen saturation during the 6 min it was recorded (Table 2, Fig. 7).

The intravenous flumazenil was well tolerated in all cases. One subject kindly agreed to let us study him on a second occasion, without having an actual endoscopy following midazolam. As can be seen from comparing Fig. 8 with Fig. 4 and 6, the midazolam-induced respiratory depression was similar on the two occasions. On both occasions he woke up promptly following flumazenil, but the midazolam-induced respiratory depression was slow to reverse.

DISCUSSION

This study confirms the finding in our previous larger studies (10–12) that intravenous midazolam in the doses used to sedate patients prior to endoscopy procedures produces respiratory depression and a significant fall in both minute volume and oxygen saturation. A recent study gave evidence to suggest that midazolam in sedation dosage might significantly depress hy-

Table 2

Mean ± s.d. and individual oxygen saturation results in 13 patients before (B) and after intravenous midazolam (PM). Also oxygen saturation recorded following removal of the endoscope, i.e. before flumazenil (BF) and then 1 min after administration of 0.5 mg of intravenous flumazenil (F.0.5). Further oxygen saturation measurements were made every minute as flumazenil was administered at $0.1\ mg \cdot min^{-1}$ up to a total of 1.0 mg (F.0.6–F.1.0). A final measurement was made 1 min later (Final). Unfortunately the data on subjects nos. 6 and 12 are incomplete because of failure of the pen recorder at the times indicated with an asterisk.

Subject	B	PM	BF	F.0.5 mg	F.0.6 mg	F.0.7 mg	F.0.8 mg	F.0.9 mg	F.1.0 mg	Final
1	93.0	88.0	93.0	93.0	93.0	93.0	95.0	95.0	95.0	95.0
2	96.0	96.0	96.0	96.0	96.0	96.0	96.0	96.0	96.0	96.0
3	99.0	99.0	95.0	96.0	99.0	98.0	97.0	97.0	97.0	97.0
4	95.0	94.0	95.0	93.0	95.0	95.0	95.0	95.0	95.0	95.0
5	93.0	91.0	91.0	91.0	89.0	90.0	90.0	90.0	91.0	91.0
6	94.0	93.0	87.0	87.0	*	*	*	*	*	86.0
7	96.0	94.0	95.0	95.0	96.0	96.0	96.0	96.0	96.0	96.0
8	94.0	92.5	92.0	90.5	89.0	91.5	92.0	92.0	92.5	93.0
9	93.0	89.0	90.0	90.0	90.5	91.0	91.0	91.0	91.0	91.0
10	97.0	97.0	96.0	96.0	96.5	96.5	96.0	96.0	96.0	96.5
11	96.0	95.0	97.0	96.5	96.5	96.5	97.0	96.5	96.5	95.5
12	90.0	91.0	87.5	86.5	87.0	90.0	*	*	*	89.0
13	95.0	91.5	90.0	90.0	90.0	91.0	91.0	91.0	91.0	91.0
Mean	94.7	93.2	92.7	92.5	93.1	93.7	94.3	94.1	94.3	93.2
s.d.	2.3	3.1	3.3	3.5	3.9	2.9	2.8	2.6	2.4	3.4

* Trace unsatisfactory for estimation of oxygen saturation because of failure of pen recorder.

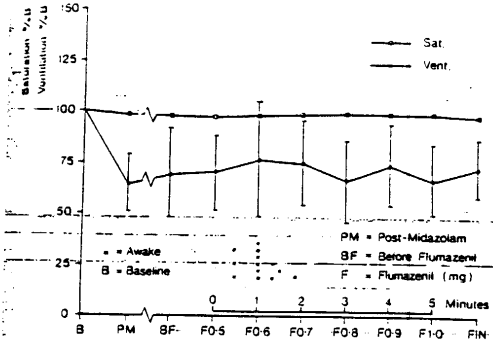

Fig. 7. Oxygen saturation and chest movements recorded continuously using an ear oximeter and induction plethysmograph respectively. Oxygen saturation and estimated ventilation are here expressed as mean ± standard deviation of base line in the 13 patients whose individual data are shown in Tables 1 and 2. Note that the mean estimated minute volume was under 75% of base line following intravenous midazolam. After completion of the gastroscopy and removal of the endoscope, the estimated ventilation was still under 75% of base line. All 13 subjects were awake within 2 min of being given 0.5 mg of flumazenil and then 0.1 mg · min^{-1} up to a total of 1.0 mg (as indicated by the individual * symbols). However, despite being awake the midazolam-induced effect on ventilation was not noticeably reversed, even after 6 min observation.

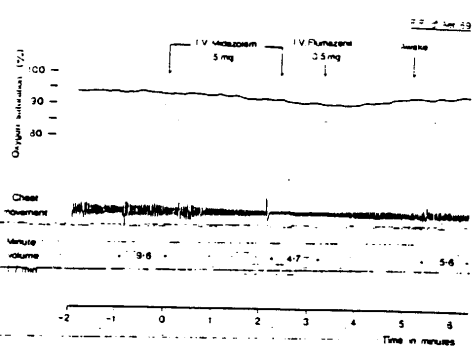

Fig. 8. Oxygen saturation and chest wall movements continuously monitored using an ear oximeter and induction plethysmograph respectively. Patient FF (see also Fig. 4–6) agreed to a repeat study to observe the effect of flumazenil on midazolam-induced respiratory depression, but without having a gastroscopy on this occasion. Again a depression of minute volume and slight fall in oxygen saturation as a result of intravenous midazolam was observed. Following intravenous flumazenil the patient awoke within 2 min, but the midazolam-induced depression of his minute volume was slow to correct.

poxic ventilatory drive in man (29). The authors recommended that oxygen saturation should be continuously monitored in all patients who are sedated with midazolam (29). We would agree with this (12), particularly if a midazolam/narcotic combination is used since oxygen saturation can fall alarmingly in this situation (23).

We were surprised to observe that, although intravenous flumazenil rapidly reversed most of the sedative effect of midazolam, with all our patients apparently wide awake within 2 min, the ventilatory depressant effect of midazolam was little affected. Mora and colleagues (30) have recently studied the sedation and ventilatory effects of midazolam at the time of colonoscopy and its reversal with flumazenil. Interestingly, again although the flumazenil effectively reversed the sedative effects of midazolam, CO_2 responsiveness was actually decreased by flumazenil and remained so for 60 min. The authors suggest this apparent respiratory depressant effect of flumazenil may result from either a dose-related interaction with midazolam or an agonistic action at another site, i.e. flumazenil may possess agonist-antagonist properties in patients (30).

Whatever the final mechanism turns out to be, it seems clear that the advice anaesthetists should give endoscopists and dentists who use intravenous midazolam to sedate their patients is as follows: a) Clinical assessment is not an adequate method of detecting early respiratory depression and hypoxia – hence non-invasive techniques such as oximetry should be much more readily available (28). b) All elderly and at-risk patients should be pre-oxygenated and given supplemental oxygen throughout the procedure (27). c) Although intravenous flumazenil is a very valuable drug and should now be available on the emergency drug trolley of all clinicians using intravenous benzodiazepines, its effect on reversing midazolam-induced ventilatory depression is slow in an emergency situation. Hence if a patient goes blue and stops breathing following intravenous benzodiazepine administration, it is still of paramount importance to (i) give oxygen, (ii) maintain an adequate airway and (iii) if necessary, start C.P.R. *before* giving intravenous flumazenil. To waste valuable time drawing up and giving flumazenil instead of attending to the above simple fundamentals may have serious and potentially fatal consequences.

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