Midazolam sedation to produce complete amnesia for bronchoscopy: 2 years' experience at a district general hospital

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Patients may find bronchoscopy unpleasant. There is some evidence that patient satisfaction correlates with amnesia for the procedure. For several years we have used doses of midazolam sufficient to put patients lightly asleep hoping to produce complete amnesia. We looked at practical aspects of this technique over a 2-year period.

We studied 337 consecutive patients. They were 219 men and 118 women of mean age 63 ± 12.4 (SD). Sixty-seven patients were aged 75 years or over and the eldest was 86. Sixty-three patients were already hospital inpatients but the remainder were seen as day cases. Midazolam was given by slow i.v. injection over several minutes until the patient was judged to be lightly asleep. Patients were given supplemental oxygen (3 l min⁻¹) and monitored by ECG and pulse oximetry. A note was made of the time at which they awakened, defined as when nursing staff felt the patients were awake enough to have a cup of tea and toast. Patients were asked if they had any memory of the procedure both on awakening and when seen a few days later to discuss the results. The procedures were carried out in a well-staffed Day Case Unit with a recovery area.

The mean dose of midazolam used was 10.8 mg (mean ± SD=0.16 ± 0.095 mg kg⁻¹). The midazolam was given over a median of 4 min (range 1-15 min). Patients took 59 ± 45 min (mean ± SD) to wake up. Twenty-eight patients were given flumazanil to reverse the sedation (11 for concern over bleeding following biopsies, three for desaturation during and three after procedure, four as they were frail, two as they were restless, two as they were hypotensive after procedure and three for miscellaneous reasons). Only nine patients could remember any part of the procedure.

Incremental doses of midazolam given slowly until patients are lightly asleep almost invariably produce complete amnesia for bronchoscopy. This is a safe technique but patients need careful monitoring and may require reversal of sedation with flumazenil.

Introduction

Patients may find bronchoscopy unpleasant (1–3). There is some evidence that patient satisfaction correlates with amnesia for the procedure (4–7). For several years, therefore, we have used intravenous midazolam in doses sufficient to put patients lightly asleep, hoping to produce complete amnesia for the procedure. We have previously described our experience (7) using an average dose of 0.24 mg kg⁻¹, but over the years have tended to use smaller doses, while still aiming to put patients asleep. We looked at practical aspects of this technique over a 2-year period.

Methods

We studied 337 consecutive patients undergoing a fiberoptic bronchoscopy between February 1996 and 1998. Sixty-three patients were already inpatients but the remainder were treated as day cases. Patient details are given in Table 1.

No patient was taking anticoagulants but aspirin therapy was not discontinued in those patients already on it. A coagulation screen was not routinely performed before the procedure.

Patients were given no premedication. The procedure consisted of approximately 5 ml of 1% lignocaine jelly placed into each nostril and then administration of midazolam by slow intravenous (i.v.) injection through an indwelling catheter over several minutes until the patient was judged to be lightly asleep, i.e. eyes closed, not responding to speech nor a mildly painful stimulus (rubbing on the sternum). Patients were given supplemental oxygen at 3 l min⁻¹ by nasal prongs. This was usually directed into the mouth, except in eight patients in whom it proved
impossible to pass the bronchoscope through the nose. For these patients the bronchoscope was inserted through the mouth and the oxygen directed into the nostrils. Patients were monitored for oxygen saturation, pulse rate and possible arrhythmias (Nellcor monitor MDE escort E300; Nellcor Puritan Bennett UK Ltd; Oxon, UK). Alarms were set to go off if the saturation fell below 90% or the pulse was below 55 or above 130.

We sprayed 4 ml of 2% lignocaine onto the vocal cords before the bronchoscope was passed through the larynx and 2 ml aliquots of 2% lignocaine were used to control coughing.

A note was made of the times (to the nearest min) of the start of the midazolam injection, beginning and end of the bronchoscopy and when the patient awoke (defined as when nursing staff felt the patient was awake enough to have a cup of tea and toast). Patients were asked if they had any memory of the procedure both shortly after awakening and again when seen to discuss the results, usually a few days later.

The procedures were carried out in a well-staffed Day Case Unit. There were at least two and usually three nurses available to help in the endoscopy room. After bronchoscopy patients were monitored in a recovery area and supplemental oxygen continued until the patients were awake. Full resuscitation facilities were available.

All patients had been advised not to drive themselves home nor to spend the night following the bronchoscopy alone. In patients suspected of having lung cancer, samples were taken in the following order: brushings for cytology; biopsies (at least six), washings for cytology. Transbronchial and transbronchial needle aspiration biopsies were not taken. However, when the bronchoscopy findings were normal but the chest X-ray suggested lung cancer, biopsies were taken blindly from the segment of the bronchial tree in which the abnormality was suspected. Some of these would go through the bronchial wall and therefore be 'transbronchial'.

The study was approved by our local Ethical Committee.

### Results

All bronchoscopies except two were successfully completed. One patient proved impossible to sedate adequately. In another bleeding following biopsy necessitated abandoning the procedure and reversing the sedation with flumazenil.

Details of midazolam dosage and timing are given in Table 1.

Total doses were similar for men and women (two-sample t-test; \( P=0.95 \)), but higher for the latter on a mg kg\(^{-1} \) basis (\( P=0.016 \)). Patients aged 75 years and over received smaller doses than younger patients (0.13 vs. 0.17 mg kg\(^{-1} \); \( P=0.0004 \)). For this age group, doses of midazolam were similar for men and women whether expressed as total dose (mean 7.46 vs. 7.95 mg; \( P=0.77 \)) or mg kg\(^{-1} \) (mean 0.12 vs. 0.15; \( P=0.27 \)). Length of injection was similar for men and women (means=4.56 vs. 4.2 min; \( P=0.29 \)). There was a negative correlation between dose in mg kg\(^{-1} \) and age for both men and women (Pearson's correlation coefficient = -0.418 and -0.407; \( P<0.001 \) for both).

For women there was a positive correlation between the dose of midazolam in mg kg\(^{-1} \) and time taken to awaken (Pearson's correlation coefficient = 0.418 and 0.407; \( P<0.001 \) for both).

Nine patients (two men, seven women; mean age 62.3 years, range 48-81) had some memory of the procedure, six on awakening and three when seen a few days later, although by then only one of the original six could remember any of the procedure.

One patient, when questioned just after the procedure, thought that he could remember the entire process, but a few days later could remember only some coughing. Other patients remembered some aspects, e.g. pain in the nose, a scraping sensation, coughing or some struggling. The doses used in these nine patients (0.12 ± 0.029 mg kg\(^{-1} \)) were similar to doses in other patients who had no memory of the procedure, although when comparing these nine

### Table 1. Patient and midazolam details

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<tr>
<th>Description</th>
<th>Total patients (( n ))</th>
<th>Men (( n ))</th>
<th>Women (( n ))</th>
<th>Mean age (± SD)</th>
<th>Range</th>
<th>Aged 75 and over (( n ))</th>
<th>Mean dose of midazolam</th>
<th>Range</th>
<th>Combined male and female ± SD</th>
<th>Timing (min)</th>
<th>Length of midazolam injection</th>
<th>Length of bronchoscopy</th>
<th>Time to awakening (from end of bronchoscopy)</th>
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<td>219</td>
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<td>Time to awakening (from end of bronchoscopy)</td>
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</table>

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**Results**

All bronchoscopies except two were successfully completed. One patient proved impossible to sedate adequately. In another bleeding following biopsy necessitated abandoning the procedure and reversing the sedation with flumazenil.

Details of midazolam dosage and timing are given in Table 1.

Total doses were similar for men and women (two-sample t-test; \( P=0.95 \)), but higher for the latter on a mg kg\(^{-1} \) basis (\( P=0.016 \)). Patients aged 75 years and over received smaller doses than younger patients (0.13 vs. 0.17 mg kg\(^{-1} \); \( P=0.0004 \)). For this age group, doses of midazolam were similar for men and women whether expressed as total dose (mean 7.46 vs. 7.95 mg; \( P=0.77 \)) or mg kg\(^{-1} \) (mean 0.12 vs. 0.15; \( P=0.27 \)). Length of injection was similar for men and women (means=4.56 vs. 4.2 min; \( P=0.29 \)). There was a negative correlation between dose in mg kg\(^{-1} \) and age for both men and women (Pearson's correlation coefficient = -0.418 and -0.407; \( P<0.001 \) for both).

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One patient, when questioned just after the procedure, thought that he could remember the entire process, but a few days later could remember only some coughing. Other patients remembered some aspects, e.g. pain in the nose, a scraping sensation, coughing or some struggling. The doses used in these nine patients (0.12 ± 0.029 mg kg\(^{-1} \)) were similar to doses in other patients who had no memory of the procedure, although when comparing these nine
Table 2. Patients who were admitted following bronchoscopy

<table>
<thead>
<tr>
<th>Reason for admission (n)</th>
<th>Total (n=11, seven men, four women)</th>
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<tbody>
<tr>
<td>Mean age (years)</td>
<td>67.6</td>
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<tr>
<td>Range</td>
<td>59-82</td>
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<tr>
<td>Mean dose of midazolam (mg) ± sd</td>
<td>8.8 ± 3.2</td>
</tr>
<tr>
<td>Range</td>
<td>3.5-14.0</td>
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<tr>
<td>mg kg⁻¹ ± sd</td>
<td>0.12 ± 0.043</td>
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<tr>
<td>Range</td>
<td>0.06-0.2</td>
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</table>

*Procedure abandoned.

Eleven out of the original 274 day case patients were admitted following the bronchoscopy. Details are given in Table 2. Overall these patients were given smaller doses of midazolam than the whole group (0.12 vs. 0.16 mg kg⁻¹; P=0.013).

Flumazenil was used to reverse sedation in 28 patients. The dose of flumazenil used was between 250 and 500 mcg, with most patients receiving 500 mcg. Details are given in Table 3. Patients given flumazenil tended to be given smaller doses of midazolam than patients who were not (mean 0.14 vs. 0.16 mg kg⁻¹; P=0.27) and were older (mean age 70.2 vs. 62.9 years; P=0.0009). Of the four patients who were hypotensive post-procedure two were taking diltiazem, two ACE inhibitors, and all four diuretics.

Of patients admitted or given flumazenil because of bleeding, all except three had biopsies. None had a clear history of alcohol excess but three had abnormal liver function tests. One was taking aspirin.

We looked separately at patients given 20 mg or more of midazolam (approximate mean +2 SD). Details are given in Table 4. Compared to patients given lower doses, they were not heavier (mean weight 69.9 vs. 69.5 kg; P=0.88), but were much younger (mean age 48.9 vs. 64.5 years; P=0.0000). They tended to take longer to awaken (mean 85.1 vs. 56.6 min; P=0.0000). The midazolam injections were given over a longer period than for patients with lower doses (mean 6.6 vs. 4.2 min; P=0.0007) but in only four patients was the injection given over 10 min or more. In two patients the sedation was reversed with flumazenil, because they seemed particularly restless post-procedure. None of these patients needed admission. Four were taking regular benzodiazepines, four opioids and 14 (including two on benzodiazepines) had a history suggestive of excess alcohol consumption. Of these, 10 had abnormal liver function tests.

The group included one woman who was a known alcoholic in whom it proved impossible to achieve adequate sedation, even when giving 45 mg total dose over a period in excess of 15 min.

Of the patients, 131 were found to have lung cancer and the remainder a variety of non-malignant conditions.

**Discussion**

We have shown over a 2-year period that patients can be safely sedated for bronchoscopy with incremental doses of midazolam.
midazolam given over several minutes until they are judged to be lightly asleep. However, we carried out the procedures in a well-staffed day case unit with a recovery area and full resuscitation facilities.

Using this technique, patients rarely have any memory of the procedure. It is not clear why a small number (less than 3%) could remember part of it. Although they were given smaller doses of midazolam than the group as a whole, the doses were similar to those given to other patients who remembered nothing and they were all judged to be lightly asleep at the onset of the procedure. None of these patients were known to have other factors which might have influenced the metabolism of midazolam, such as an excess alcohol intake or concomitant use of benzodiazepines or rifampicin (8).

Little is known about patients' fears concerning bronchoscopy, although a Malaysian study (9) showed that over 80% of patients preferred to be sedated and only rarely did patients have a fear of sedation. However, no studies have been carried out comparing patients' views of bronchoscopy while unsedated compared to bronchoscopy under sedation given in sufficient doses to produce complete amnesia, but there is a suggestion both for endoscopy (1, 5) and bronchoscopy (6, 7) that patient acceptability correlates with the level of amnesia for the procedure.

We admitted 11 out of 274 patients in whom the procedure had been planned as a day case. Of these, two were for pre-existing conditions (chest pain due to metastases and a pleural effusion) but most were due to concern over bleeding following biopsies. The sedation technique may have contributed to the admission of five patients; two desaturated in association with bleeding and the development of atrial fibrillation, two patients desaturated associated with bleeding and one desaturated after the end of the procedure. Social factors contributed to the decision to admit at least two of the patients.

Flumazenil was used to reverse sedation in 28 patients, usually because of concern over bleeding, but also in four patients who were hypotensive post-procedure. Drug interactions, including diltiazem which inhibits the metabolism of midazolam (8), may also have contributed. We admitted four elderly patients who seemed particularly frail. Although flumazenil has a shorter half-life than midazolam and resedation may occur (10) we found a second dose of flumazenil to be necessary in only one patient.

During the procedure we used boluses of lignocaine to suppress coughing which made the procedure difficult for the operator. We did not keep records of the precise dose used, but the technique was identical to that which we have used for some years and described previously (11) therefore the doses were unlikely to be excessive.

Complications may be more common when bronchoscopy is carried out in patients with severe obstructive pulmonary disease (12). Our study does not allow us to draw any conclusions about the safety of midazolam sedation in this group of patients. We used the same technique for all patients undergoing a bronchoscopy, while spirometry was often not available. Over the 2-year period bronchoscopy was not carried out in a few patients who were judged by the operator (T.J.W.) to be high-risk, e.g. patients who looked particularly frail or who were required continuous oxygen therapy. The decision not to perform bronchoscopy was usually based on a subjective clinical impression rather than objective data.

One disadvantage of the technique is that some patients take a long time to awaken. This may reflect the prolonged elimination half-life of midazolane which occurs in some patients (13). It is not clear why there was a better correlation between dose and time to awakening in women than in men.

Alcohol intake and liver function may influence the clinical effect of midazolam. These factors were not known in all our patients. However, in the group requiring 20 mg or more of midazolam, at least half had a history suggestive of excessive alcohol consumption.

Our study does not allow us to draw conclusions as to the minimum dose that can be used to produce complete amnesia. We have previously shown that a higher dose (mean 0.24 mg kg$^{-1}$) (7) invariably produces amnesia. Other studies showed that 0.03 mg kg$^{-1}$ for fiberoptic bronchoscopy (14), rigid bronchoscopy (15) and endoscopy (4) frequently did not produce amnesia. Similarly, 0.07 mg kg$^{-1}$ for endoscopy (16) and 0.1 mg kg$^{-1}$ for rigid bronchoscopy (15) again did not always produce amnesia, although a higher dose (mean 0.17 mg kg$^{-1}$) used for fiberoptic bronchoscopy did (17). This latter dose is similar to the dose used in our present study.

It is not certain how to assess clinically when a patient has had a sufficient dose of midazolam to produce complete amnesia. In this study we chose the point at which the patient seemed to be lightly asleep, as when using higher doses (7) we had shown this clinical feature to correlate with complete amnesia. Complete amnesia was produced giving incremental doses up to the onset of ptosis (17) but in this study additional maintenance doses were given during the procedure. Another endoscopy study (5) which used the clinical signs of onset of slurred speech, nystagmus or ptosis, only produced complete amnesia in 73% of patients. Additional doses were also sometimes given during the procedure.

An important aspect of giving intravenous midazolam may be the speed of the injection. The blood-brain equilibration is slow (18) and may take up to 3 min for maximum effect (19). Therefore, it may be best to give midazolam in small incremental doses and waiting 2–3 min between each dose. Although we deliberately tried to give the injection slowly over several minutes, the median time was only 4 min and it is possible that we might have been able to produce complete amnesia with lower doses given more slowly. This might also have avoided the particularly high doses given to some patients. However, in a study of only 20 patients who were given small doses at 2-minute intervals, the total doses required (induction plus maintenance doses) were similar to those used in our study (17).

In summary, we have shown over a 2-year period that incremental doses of midazolam given until a patient is lightly asleep is a safe technique for bronchoscopy and almost invariably produces complete amnesia. However,
patients need careful monitoring and may require reversal of sedation with flumazenil.

Acknowledgements

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References