COMPARISON OF DIAZEPAM AND MIDAZOLAM FOR SEDATION DURING LOCAL ANAESTHESIA FOR BRONCHOSCOPY

K. KORTTILA AND J. TARKKANEN

Local anaesthetic techniques are preferable to the use of general anaesthesia in outpatients for procedures such as bronchoscopy, since patients require less supervision in the period after operation (Korttila, 1981). Bronchoscopy under local anaesthesia necessitates reliable sedation of short duration to make the procedure more acceptable to the patient (Korttila et al., 1978a). Hitherto, diazepam has been recommended for such sedation (Editorial, 1976; Korttila, 1980a). Recently, it has been suggested that the relatively new benzodiazepine midazolam might be preferable for sedation during short procedures: its effects have been reported to be of shorter duration than those of diazepam (Dornauer and Aston, 1983; Editorial, 1983), its salts are water-soluble, and it causes pain or venous thrombosis only occasionally.

We have previously compared diazepam and flunitrazepam, and have evaluated the relationship between age, amnesia and sedation during local anaesthesia for bronchoscopy (Korttila et al., 1978a, b). Although the suitability of midazolam for use in gastroscopy has been extensively studied (Al-Khudhairi, Whitwam and McCloy, 1982; Brophy et al., 1982; Berggren et al., 1983; Magni et al., 1983), there have been no reports on the utility of midazolam during bronchoscopy. The purpose of the present study was to compare i.v. diazepam and midazolam as amnesic and sedative adjuncts to local anaesthesia for bronchoscopy, with particular attention to the rapidity of recovery after sedation achieved with clinically comparable doses of the drugs.

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SUMMARY
Bronchoscopy was performed in 76 outpatients using local anaesthesia plus diazepam 0.2 mg kg\(^{-1}\) i.v. or midazolam 0.05 or 0.1 mg kg\(^{-1}\) i.v. Patient co-operation and ease of bronchoscopy were good in all patients. Two hours after injection, 67% (diazepam 0.2 mg kg\(^{-1}\)), 36% (midazolam 0.05 mg kg\(^{-1}\)) and 75% (midazolam 0.1 mg kg\(^{-1}\)) of the patients failed to recall the insertion of the bronchoscope. Similarly, when asked on the following day, only 22%, 52% and 8%, respectively, of the patients remembered bronchoscopy. Two hours after sedation, the patients' performances in three psychomotor tests were similar to those measured before sedation in each group, but the patients' ability to stand steadily and walk along a straight line reverted to normal significantly (P < 0.05) more slowly in patients receiving midazolam 0.1 mg kg\(^{-1}\) than in the patients given diazepam. The results suggest that midazolam offers no advantage over diazepam in terms of speed of recovery of psychomotor function, when doses of similar potency are given for bronchoscopy.

PATIENTS AND METHODS
Sedation
Seventy-six outpatients undergoing diagnostic, open, rigid bronchoscopy were admitted to the study. The patients were randomly allocated to three groups, which were similar as regards age, weight and height (table I). Any patient who had received a psychotropic drug or any other drug known to interact with benzodiazepines, or who could not perform the recovery tests before the drugs were administered, was excluded. The plan of investigation was approved by our institutional ethics committees, and informed consent was obtained from each patient.
Topical anaesthesia of the respiratory tract was produced by the administration of lignocaine using an ultrasonic nebulizer (Korttila, Tarkkanen and Tarkkanen, 1981). Fifteen millilitre of 4% lignocaine solution was introduced to the nebulizer chamber, and was atomized by oxygen for inhalation. Nebulization was continuous for 15 min during inspiration and expiration. The inhalation anaesthesia was supplemented using three 10-mg aliquots of 10% lignocaine solution, two sprayed into each vallecula and one on the epiglottis. Atropine 0.01 mg kg\(^{-1}\) was injected i.v. and, 5 min later, the sedative was administered: diazepam 0.2 mg kg\(^{-1}\) was injected to a cubital vein at a rate of 10 mg min\(^{-1}\), or midazolam 0.05 or 0.1 mg kg\(^{-1}\) was given at the rate of 5 mg min\(^{-1}\). The patient, the bronchoscopist and the investigator were all unaware of the identity of the drug being administered.

Clinical observations, assessment of amnesia and subjective assessments

Systolic and diastolic arterial pressures were measured by auscultation, and the heart rate was counted at the wrist before, during and after the procedure (Korttila et al., 1978a).

Amnesia was assessed 2 h after injection of the sedative, when each patient was asked if he or she recalled insertion and removal of the bronchoscope. To evaluate the duration of the amnesic effect, we made additional use of two of the tests of clinical recovery: the patients were asked, 1 h and 2 h after injection of the sedative, if they could remember that their ability to stand steadily had been tested at 30 min, and their ability to walk along a straight line at 60 min, respectively.

The bronchoscopist rated both the adequacy of anaesthesia and patient co-operation (ease of bronchoscopy) using visual analogue scales from poor to good. The patient rated the acceptability of the procedure in the same manner.

Evaluation of recovery

The clinical recovery of the patient was determined using Romberg's test and by the patient's ability to walk along a straight line (Korttila, 1976). Assessments were made when the patient arrived in the operating theatre and 30, 60 and 120 min after the injection of the sedative.

Visualization test (James, 1969). The subject was required to trace each of 10 intermingled lines from their origins on the left side of a page to their termination on the right, without the aid of a finger. The score was the number of correct tracings per 3-min period.

Aiming test (James, 1969). A piece of paper (20 cm \times 30 cm) with 15 rows of 20 open circles (diameter 2 mm) was used. The subject had to place a dot inside each of as many circles as possible in 6 min. The dots were not to touch the edges of the circles. The score was based on the number of correct responses.

Perceptual speed test (Gelfman et al., 1979). Using a set of numbers, the patient's task was to mark all the digits in a row which were identical with the one circled at the beginning of the row. The number of correct responses during a 2-min period was scored.

The three psychomotor paper-and-pencil tests were carried out before and 2 h after injection of the sedative.

Questionnaire

Each patient received a sealed envelope containing a questionnaire concerning the bronchoscopy and the patient's opinion of its acceptability (Korttila et al., 1978a). The questionnaire was completed the day after the procedure.

Data analysis

Statistical analysis of the data was carried out using the non-parametric Chi-squared test and Student's \( t \) test for independent means between the groups and for dependent means within the groups.

RESULTS

The principal differences recorded between diazepam and midazolam were that midazolam 0.1 mg kg\(^{-1}\) induced slightly more prolonged
amnesia than diazepam 0.2 mg kg⁻¹, and that ability to walk was regained more slowly after midazolam 0.1 mg kg⁻¹ than after diazepam 0.2 mg kg⁻¹.

Cardiovascular effects and the performance of bronchoscopy

After each sedative regimen, both systolic and diastolic arterial pressures remained almost unaltered during bronchoscopy. They were slightly lower (always by less than 16 mm Hg systolic and 7 mm Hg diastolic) thereafter. Heart rates increased by an average of 10 beat min⁻¹ after each of the sedatives. The mean times (±SD) for performance of bronchoscopy varied according to the sedative used: diazepam 0.2 mg kg⁻¹, 8.3 ± 5.1 min; midazolam 0.05 mg kg⁻¹, 7.3 ± 4.0 min; midazolam 0.1 mg kg⁻¹, 9.3 ± 6.4 min.

Subjective assessments

The efficacy of local anaesthesia, patient co-operation and acceptability of the procedure to patients were similar in each experimental group (table II).

Amnesia

Amnesia to insertion and removal of the bronchoscope was significantly more common after diazepam 0.2 mg kg⁻¹ (P < 0.05) and midazolam 0.1 mg kg⁻¹ (P < 0.01) than after midazolam 0.05 mg kg⁻¹ (table III). Two hours after injection, failure to recall removal of the bronchoscope was recorded for 70% of patients who received diazepam 0.2 mg kg⁻¹, 40% of those who received midazolam 0.05 mg kg⁻¹ and 83% of those receiving midazolam 0.1 mg kg⁻¹. The amnesic action of midazolam 0.1 mg kg⁻¹ lasted longer than that of diazepam 0.2 mg kg⁻¹. Twenty-three per cent of patients who received midazolam 0.1 mg kg⁻¹ did not remember that Romberg’s test had been performed at 30 min, when questioned 60 min after injection. Only 4% of patients receiving diazepam did not remember Romberg’s test (table III).

Recovery

The patient’s ability to stand steadily and walk along a straight line became normal significantly (P < 0.05 to P < 0.01) more slowly in those who received midazolam 0.1 mg kg⁻¹ than in patients who received midazolam 0.05 mg kg⁻¹ or diazepam (table IV). Thirty minutes after the injection, 56%,

<table>
<thead>
<tr>
<th>TABLE II. Efficacy of local anaesthesia and patient co-operation during bronchoscopy (0 = poor, 100 = good) and acceptability of procedure determined after 2 h (0 = unpleasant, 100 = pleasant). (Mean values ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Diazepam 0.2 mg kg⁻¹ (n = 27)</td>
</tr>
<tr>
<td>Midazolam 0.05 mg kg⁻¹ (n = 25)</td>
</tr>
<tr>
<td>Midazolam 0.1 mg kg⁻¹ (n = 24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE III. Amnesia for bronchoscopy and for recovery tests 2 h afterwards (% of total). *P &lt; 0.05 and **P &lt; 0.01 v. midazolam 0.05 mg kg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Diazepam 0.2 mg kg⁻¹ (n = 27)</td>
</tr>
<tr>
<td>Midazolam 0.05 mg kg⁻¹ (n = 25)</td>
</tr>
<tr>
<td>Midazolam 0.1 mg kg⁻¹ (n = 24)</td>
</tr>
</tbody>
</table>
TABLE IV. Percentage of patients who could not stand steadily or walk along a straight line 30, 60 and 120 min after injection of diazepam or midazolam. *P < 0.05 v. midazolam 0.05 mg kg⁻¹; **P < 0.01 v. diazepam and midazolam 0.05 mg kg⁻¹; ***P < 0.05 v. diazepam

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Unable to stand steadily after</th>
<th>Unable to walk along a straight line after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Diazepam 0.2 mg kg⁻¹ (n = 27)</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>Midazolam 0.05 mg kg⁻¹ (n = 25)</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Midazolam 0.1 mg kg⁻¹ (n = 24)</td>
<td>67*</td>
<td>17</td>
</tr>
</tbody>
</table>

TABLE V. Recovery (visualization, aiming and perceptual speed tests). Mean values ± SD before sedation and 2 h afterwards

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visualization test, numbers correct</th>
<th>Aiming test, numbers correct</th>
<th>Perceptual speed test, numbers correct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before sedation</td>
<td>After 2 h</td>
<td>Before sedation</td>
</tr>
<tr>
<td>Diazepam 0.2 mg kg⁻¹</td>
<td>9.5 ± 1.0</td>
<td>9.0 ± 1.8</td>
<td>231 ± 62</td>
</tr>
<tr>
<td>Midazolam 0.05 mg kg⁻¹</td>
<td>9.1 ± 2.0</td>
<td>8.5 ± 2.2</td>
<td>207 ± 67</td>
</tr>
<tr>
<td>Midazolam 0.1 mg kg⁻¹</td>
<td>9.0 ± 2.5</td>
<td>8.5 ± 2.8</td>
<td>223 ± 49</td>
</tr>
</tbody>
</table>

32% and 67% of patients receiving diazepam 0.2 mg kg⁻¹, midazolam 0.05 mg kg⁻¹ or midazolam 0.1 mg kg⁻¹, respectively, were unable to stand steadily. At 60 min, the corresponding figures for patients unable to walk along a straight line were 22%, 20% and 58%. All patients who had received diazepam were able to walk along a straight line 2 h after the injection, but 17% of patients receiving midazolam 0.1 mg kg⁻¹ were unable to do so (table IV).

With the visualization, aiming and perceptual speed tests, there were no differences between patients of different sedative treatment groups (table V). Two hours after sedation, the patient's psychomotor performance in each test was similar to that measured before sedation.

**Questionnaire**

The acceptability of both sedation and the procedure were confirmed in each group (table VI). No retrograde amnesia was associated with diazepam or midazolam administration. On the day after diazepam 0.2 mg kg⁻¹ and midazolam 0.1 mg kg⁻¹, only 22% and 8% of patients, respectively, remembered bronchoscopy having been performed. After midazolam 0.05 mg kg⁻¹, the figure was 52%.

TABLE VI. Answers to the questionnaire (% of totals). *P < 0.05 and **P < 0.01 v. midazolam 0.05 mg kg⁻¹

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remembered</th>
<th>Local anaesthesia</th>
<th>Insertion of needle</th>
<th>Bronchoscopy</th>
<th>Would like next bronchoscopy performed similarly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam 0.2 mg kg⁻¹</td>
<td>26</td>
<td>100</td>
<td>100</td>
<td>26*</td>
<td>85</td>
</tr>
<tr>
<td>Midazolam 0.05 mg kg⁻¹</td>
<td>89</td>
<td>96</td>
<td>96</td>
<td>8</td>
<td>85</td>
</tr>
<tr>
<td>Midazolam 0.1 mg kg⁻¹</td>
<td>36</td>
<td>100</td>
<td>100</td>
<td>28</td>
<td>85</td>
</tr>
</tbody>
</table>

**DISCUSSION**

We wanted to assess midazolam as an i.v. sedative because findings during gastroscopy (Al-Khudhairi, Whitwam and McCloy, 1982; Brophy et al., 1982; Berggren et al., 1983; Bardhan et al., 1982) had indi-
cated that midazolam might be preferable to diazepam for inducing mild sedation during short procedures.

The practice of early discharge of patients from hospital after outpatient procedures highlights the need to test for recovery after sedation. Both Romberg's test and the test of capacity to walk along a straight line are easy to perform, and are indices of the co-ordination skills which are affected to the greatest degree, and for the longest time, after sedation with benzodiazepines (Korttila and Linnoila, 1975, 1976; Korttila et al., 1978a). These tests obviously do not indicate "street-fitness" or full psychomotor recovery, but can help clinicians to reach a decision regarding the discharge of patients after sedation or anaesthesia (Korttila, 1981).

Visualization and aiming tests have been shown to be sensitive measures of mental function after cyclopropane anaesthesia (James, 1969) and flunitrazepam sedation (Korttila et al., 1978b). Scores in the perceptual speed test have been shown to be impaired after sedation with diazepam and i.v. anaesthetics (Gelfman et al., 1979; Korttila et al., 1981). We used these tests to study differences between recovery in various treatment groups, but found that, after midazolam, walking along a straight line was a more sensitive index of recovery than were these psychomotor tests.

Amnesia is less frequent to tactile stimuli than to events or visual stimuli following the administration of diazepam (Korttila, 1980a). Bronchoscopy is a frightening and powerful tactile stimulus, and is easy to remember, which may explain why we did not find the greater degree of amnesia following midazolam, compared with diazepam, observed by other investigators (Whitwam, Al-Khudhairi and McCoy, 1983; Dixon et al., 1984).

Our aim was to study doses of diazepam and midazolam which were similar in respect of amnesic action, and to compare side effects and recovery after such doses. Since the amnesia to bronchoscopy with diazepam 0.2 mg kg\(^{-1}\) proved similar in this study to that with midazolam 0.1 mg kg\(^{-1}\), we considered comparison of rates of recovery after the two benzodiazepines at these doses to be justified.

Midazolam disappears from the blood much faster than diazepam. Its half-life (mean ±SD) during the elimination phase has been reported to be 2.4 ± 0.8 h (Allonen, Ziegler and Klotz, 1981) and 1.77 ± 0.83 h (Smith, Eadie and O'Reourke-Brophy, 1981). That for diazepam is considerably longer (20–60 h) (Korttila, 1980b). However, recent clinical studies, and our results, suggest that the rapid disappearance of midazolam from the blood is not associated with rapid recovery. Dixon and others (1984) found no difference in the rate of recovery using the Trieger test in patients receiving midazolam 0.08 mg kg\(^{-1}\) or diazepam 0.15 mg kg\(^{-1}\) i.v. to supplement regional blocks. Whitwam, Al-Khudhairi and McCoy (1983) reported recovery as assessed by Romberg's test to be similar after midazolam and diazepam at doses comparable in potency, given for gastroscopy. Kawar and colleagues (1982), using a pegboard test, found a similar recovery time in patients receiving midazolam 0.1 mg kg\(^{-1}\) or diazepam 0.2 mg kg\(^{-1}\) i.v. as a sedative in dentistry.

Our finding that the ability of patients to stand steadily and walk along a straight line reverted to normal more slowly after midazolam 0.1 mg kg\(^{-1}\) than after diazepam 0.2 mg kg\(^{-1}\), reflects the failure of Kawar and colleagues (1982), Whitwam, Al-Khudhairi and McCoy (1983), and Dixon and colleagues (1984) to demonstrate rapid recovery after midazolam, and suggests that testing the ability to walk along a straight line is a sensitive test for measuring the residual effects of midazolam. One explanation for the clinical finding that recovery from midazolam is not as fast as its pharmacokinetics would suggest, is that one metabolite of midazolam, α-hydroxymidazolam, has pharmacological activity. Crevoisier and others (1983) reported that α-hydroxymidazolam contributes to the central nervous system effects of midazolam, especially after oral administration.

Our conclusion is that, if doses of midazolam or diazepam, comparable in potency, are given during bronchoscopy, recovery of psychomotor function is not more rapid after sedation with midazolam than after sedation with diazepam.

REFERENCES


